2023-1169

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

AMARIN PHARMA, INC., AMARIN PHARMACEUTICALS IRELAND LIMITED, MOCHIDA PHARMACEUTICAL CO., LTD.,

Plaintiffs-Appellants,

v.

HIKMA PHARMACEUTICALS USA INC., HIKMA PHARMACEUTICALS PLC,

Defendants-Appellees,

HEALTH NET LLC,

Defendant

Appeal from the United States District Court for the District of Delaware
Case No. 1:20-cv-01630-RGA-JLH, Judge Richard G. Andrews

APPELLANTS' OPENING BRIEF

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March 21, 2023

Claim Language

’537 patent

1. A method of reducing occurrence of a cardiovascular event in a hypercholesterolemia patient consisting of:

identifying a patient having triglycerides (TG) of at least 150 mg/DL and HDL-C of less than 40 mg/dL in a blood sample taken from the patient as a risk factor of a cardiovascular event, wherein the patient has not previously had a cardiovascular event, and administering ethyl icosapentate in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor,

wherein said 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitor is administered to the patient at least one of before, during and after administering the ethyl icosapentate; and

wherein the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor is selected from the group consisting of pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin, pitavastatin, rosuvastatin, and salts thereof, and

wherein daily dose of the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor are 5 to 60 mg for pravastatin, 2.5 to 60 mg for simvastatin, 10 to 180 mg for fluvastatin sodium, 5 to 120 mg for atorvastatin calcium hydrate, 0.5 to 12 mg for pitavastatin calcium, 1.25 to 60 mg for rosuvastatin calcium, 5 to 160 mg for lovastatin, and 0.075 to 0.9 mg for cerivastatin sodium.

’861 patent

1. A method of reducing risk of cardiovascular death in a subject with established cardiovascular disease, the method comprising administering to said subject about 4 g of ethyl icosapentate per day for a period effective to reduce risk of cardiovascular death in the subject.

2. The method of claim 1, wherein the subject has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL and a fasting baseline LDL-C level of about 40 mg/dL to about 100 mg/dL.

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number 23-1169

Short Case Caption Amarin Pharma, Inc. v. Hikma Pharmaceuticals USA Inc.

Filing Party/Entity Amarin Pharma, Inc.; Amarin Pharmaceuticals Ireland; and Mochida Pharmaceuticals Co., Ltd.

Instructions: Complete each section of the form. In answering items 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance. **Please enter only one item per box; attach additional pages as needed and check the relevant box**. Counsel must immediately file an amended Certificate of Interest if information changes. Fed. Cir. R. 47.4(b).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 3/21/2023

Signature: /s/Nathan K. Kelley

Name: Nathan K. Kelley

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. ☑ None/Not Applicable	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. ☐ None/Not Applicable
Amarin Pharma, Inc.		Amarin Corporation plc
Amarin Pharmaceuticals Ireland Limited		Amarin Corporation plc
Mochida Pharmaceutical Co., Ltd.		N/A

☐ Additional pages attached

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

☐ None/Not Applicable ☐ Additional pages attached

Fish & Richardson, P.C.	Jeremy Douglas Anderson	Robert M. Oakes
Deanna J. Reichel	Elizabeth M. Flanagan	Jonathan E. Singer
Michael J. Kane		

5. Related Cases. Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). See also Fed. Cir. R. 47.5(b).

☑ None/Not Applicable ☐ Additional pages attached

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

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TABLE OF ABBREVIATIONS AND CONVENTIONS

’537 patent	U.S. Pat. No. 9,700,537
’861 patent	U.S. Pat. No. 10,568,861
Appx____	joint appendix page ____
Amarin	plaintiffs–appellants Amarin Pharma, Inc., Amarin Pharmaceuticals Ireland Ltd., and Mochida Pharmaceutical Co., Ltd., collectively
CV	cardiovascular
E-EPA	ethyl icosapentate (or icosapent ethyl)
EPA	icosapentaenoic acid
FAC	Amarin’s First Amended Complaint, Appx504-557
Hikma	defendants–appellees Hikma Pharmaceuticals USA Inc. and Hikma Pharmaceuticals PLC, collectively
HTG	hypertriglyceridemia
MTD	Hikma’s motion to dismiss first amended complaint for failure to state a claim under Fed. R. Civ. P. 12(b)(6), Appx941-968
SH	severe hypertriglyceridemia
TG	triglyceride
the asserted patents	the ’537 and ’861 patents
USPTO	United States Patent and Trademark Office
xx:*yy*-*zz*	column *xx*, lines *yy*-*zz*

RELATED CASES

No other appeals involving this civil action have been before this or any other appellate court. Appellants and their counsel are unaware of any other pending cases that will directly affect or be directly affected by the decision in this case.

INTRODUCTION

The generic drug approval scheme created by Congress permits a generic drug manufacturer like Hikma to copy the portion of a brand-name drug's label directed to a non-patented use of the drug so long as the generic manufacturer carves out any patented uses from its proposed label. If approved by the FDA, the generic manufacturer can market the drug, but only for the non-patented use indicated on the resulting "skinny label," which lists less than all the uses for which the brand-name drug has received approval. But even when the generic manufacturer proceeds with its skinny label, it still cannot encourage physicians to use the generic drug for the unauthorized, patented use that is not on the skinny label.

In this case, Hikma attempted to create a skinny label under this scheme. But Hikma, through multiple modes and media outside the label, encouraged prescribing physicians to replace Amarin's brand-name medication with Hikma's generic version for the patented use—the use for which Hikma's generic version was not approved. This was induced patent infringement.

The district court dismissed Amarin's complaint for failing to state a claim for induced infringement. In so doing, the district court misapplied the plausibility pleading standard by improperly considering Amarin's allegations in isolation instead of weighing them together; it made improper, implicit factual determinations

while bypassing the key factual dispute regarding what Hikma communicated to prescribing physicians; and it incorrectly analogized the case law.

Skinny-label precedent can involve difficult and close questions. The Court does not need to grapple with those questions here because this is not a true skinny-label case. Amarin's allegations are based not just on Hikma's label, but on its public statements made in press releases and on its website that encouraged physicians to prescribe Hikma's generic drug for an off-label use patented by Amarin. The district court erred when it considered each of those allegations one-by-one without considering whether it was at least plausible that Hikma's label together with its various public statements collectively encouraged infringement by prescribing physicians. And contrary to the district court's analysis, this Court's skinny-label precedent further supports inducement—especially *plausible* inducement—on the facts alleged. And the case law fully supports Amarin's view that the difficult questions and related factual disputes in this case cannot be resolved on a motion to a dismiss.

Reversal and remand is appropriate.

JURISDICTION

The district court had jurisdiction under 28 U.S.C. §§ 1331 and 1338(a), and entered partial final judgment pursuant to Fed. R. Civ. P. 54(b) on October 13, 2022.

Appx14-15; Appx507. Appellants filed a timely notice of appeal on November 9, 2022. Appx2069-2070. This Court has jurisdiction under 28 U.S.C. § 1295(a)(1).

STATEMENT OF ISSUES

1. Did the district court err by failing to consider the combined weight and effect of evidence demonstrating Hikma's repeated extra-label encouragement of using their generic version of Amarin's patented drug for *both* the approved skinny-label use of treating severe hypertriglyceridemia *and* the non-approved and infringing use of reducing cardiovascular risk in patients who do not suffer from severe hypertriglyceridemia when it dismissed Amarin's complaint for failure to state a claim?

2. Did the district court err by implicitly making a factual finding on the pleadings regarding what Hikma's conduct communicated to prescribing physicians, a key element of induced infringement?

3. Did the district court improperly analogize Amarin's allegations to *Grunenthal*, a label-only case where the asserted patent covered a use narrower than the generic label instructed, whereas Amarin alleged extra-label inducement activity by Hikma in the context of Amarin's patents, which are directed to a use broader than Hikma's approved use?

STATEMENT OF THE CASE

A. Vascepa® and its demonstrated efficacy for two different treatments

1. Severe hypertriglyceridemia, pancreatitis, and its treatment

Triglycerides, whether derived from food or made by the body, are a type of fat that circulates in human blood. While triglycerides are necessary for good health, high triglyceride levels, generally referred to as hypertriglyceridemia ("HTG"), can lead to serious conditions. Severe HTG[1] is a condition in which a patient's blood triglyceride level (measured in milligrams of triglycerides per deciliter of blood, i.e., mg/dL) exceeds 500 mg/dL. Appx696 (FAC, Ex. K ¶1). The primary concern with severe HTG patients is pancreatitis. Appx952 (MTD, 5); Appx866 (FAC, Ex. BB at ¶7).

Vascepa® is a prescription drug Amarin developed and markets in the United States. Appx508 (FAC, ¶28). Its active ingredient is ethyl icosapentate ("E-EPA") (sometimes referred to as icosapent ethyl), an ethyl ester of an omega-3 polyunsaturated fatty acid called icosapentaenoic acid ("EPA") that occurs in and is

[1] Severe hypertriglyceridemia, or severe HTG, was referred to as "SH" before the district court, and the corresponding indication was referred to as the "SH indication."

derived from fish oils. Appx1415 (R&R, 3); Appx40 ('537 patent, 3:14-40); Appx508 (FAC, ¶28).

Amarin initially studied Vascepa® in patients with severe HTG (the "Marine" trial). Appx508 (FAC, ¶30). The Marine trial demonstrated that Vascepa® lowers triglyceride levels in severe HTG patients without also raising levels of "bad" cholesterol, LDL-C. *Id*. That was a significant outcome because another drug indicated to reduce triglyceride levels—Lovaza®—can significantly increase bad cholesterol levels. Appx107 ('861 patent, 1:40-45). Following the Marine trial, the FDA approved Vascepa® as a treatment for severe HTG in 2012. Appx508 (FAC, ¶30). With that approval, Vascepa® became the first—and remains the only—medication approved for treating severe HTG that does not raise bad cholesterol levels. Appx508 (FAC, ¶30); *see* Appx107 ('861 patent, 1:40-45).

2. Amarin initially patented the use of Vascepa® to treat severe HTG

Amarin initially obtained patents covering only the use of Vascepa® to treat severe HTG ("the severe HTG patents"), but those patents are not at issue here. Amarin asserted the severe HTG patents against Hikma in 2017 after Hikma sought FDA approval to launch a generic form of Vascepa® for treating severe HTG. Appx980 (Opp., 6 n.2). In March 2020, the U.S. District Court for the District of Nevada found the severe HTG patents invalid as obvious, and, in September 2020, this Court affirmed without opinion. Appx948 (MTD, 1); *Amarin Pharma, Inc. v.*

Hikma Pharms. USA, Case No. 20-1723 (Fed. Cir. Sept. 3, 2020), ECF No. 78. Hikma's generic version of Vascepa® was then approved by the FDA for—and only for—treating severe HTG. JA521 (FAC, ¶82).

3. Amarin later patented the use of Vascepa® to reduce cardiovascular risk in patients with non-severe HTG or existing cardiovascular disease

Non-severe HTG, or simply HTG, broadly refers to the condition in which a patient's triglyceride level is above the normal acceptable level of 150 mg/dL, which is less than one-third the 500 mg/dL triglyceride level associated with severe HTG. The primary concern when it comes to HTG, as opposed to severe HTG, is not pancreatitis. *See* Appx952 (MTD, 5); Appx866 (FAC, Ex. BB at ¶7). Instead, patients with HTG, like those with hypercholesterolemia (high cholesterol) or those with an established cardiovascular disease, are at risk for adverse cardiovascular events like a heart attack, i.e., myocardial infarction. *See* Appx40 ('537 patent, 3:14-40). Thus, unlike severe HTG where pancreatitis is the primary concern, the primary concern for patients with HTG and elevated LDL cholesterol levels is cardiovascular risk reduction. Appx866 (FAC, Ex. BB at ¶7).

After completing the Marine trial and receiving FDA approval for Vascepa® to treat severe HTG, Amarin continued its clinical work and studied whether Vascepa® could alternatively be used to treat patients with elevated triglyceride levels (200 - 500 mg/dL) and controlled LDL cholesterol levels in what was known

as the "Anchor" trial. *See* Appx509 (FAC, ¶31); Appx871 (FAC, Ex. BB at ¶18).

When the Anchor trial was designed, it was generally accepted that lowering triglyceride levels correlated with reduced cardiovascular risk. Appx509 (FAC, ¶31); Appx866 (FAC, Ex. BB at ¶7). The Anchor trial was thus designed to study whether Vascepa—as an add-on to a common cholesterol-lowering therapy using drugs called "statins" would lower triglyceride levels in patients having HTG, but not severe HTG. Appx509 (FAC, ¶31) (explaining that the Anchor trial studied patients with triglycerides levels between 200 mg/dL and 500 mg/dL). While the Anchor trial demonstrated that Vascepa® lowered triglyceride levels in those patients, the FDA did not approve Vascepa® for cardiovascular risk reduction because it concluded, based on the results of other intervening studies, that reduced triglyceride levels were *not* correlated with reduced cardiovascular risk. Appx509 (FAC, ¶32) (citing Appx863-881 (FAC, Ex. BB)); Appx871-872 (FAC, Ex. BB at ¶¶19-20).

In view of the FDA's revised understanding that reduced triglyceride levels were not correlated with reduced cardiovascular risk, Amarin conducted a third clinical trial called the "REDUCE-IT" trial. Appx509 (FAC, ¶33). Rather than focusing on triglyceride levels, the REDUCE-IT trial studied whether Vascepa® could reduce cardiovascular events by following more than 8,000 patients over a median of five years. Appx509 (FAC, ¶33) (citing Appx832-843 (FAC, Ex. V)). As

in the Anchor trial, Vascepa® was evaluated in the REDUCE-IT trial as an add-on to statin therapy to determine its effect on reducing cardiovascular events in patients with elevated triglyceride levels (between 150 mg/dL and 499 mg/dL). Appx509 (FAC, ¶33); Appx832 (FAC, Ex. V at Methods). But unlike the Anchor trial, where results were based on measuring the patients' triglyceride levels, the REDUCE-IT trial directly studied whether Vascepa® reduced cardiovascular events by following patients with HTG and observing their clinical outcomes. *See* Appx509 (FAC, ¶33).

The REDUCE-IT trial was a success. The results, first announced in September 2018, showed a 25% further reduction in major cardiovascular events compared to patients on statin therapy alone. Appx509-510 (FAC ¶34) (citing Appx680-683 (FAC, Ex. H)). Those results were met with widespread enthusiasm and surprise in the field and were hailed as a "game changer." Appx510 (FAC ¶35) (citing Appx852-853 (FAC, Ex. Y); Appx855-857 (FAC, Ex. Z)).

Based on the success of the REDUCE-IT trial, the FDA approved Vascepa® for a second indication: as a treatment to reduce cardiovascular risk in patients with HTG. *See* Appx509-510 (FAC, ¶34) (citing Appx685-689 (FAC, Ex. I)); Appx517 (FAC, ¶62) (citing Appx674-678 (FAC, Ex. G)). The Vascepa® label thus includes two approved indications, the earlier "Severe Hypertriglyceridemia Indication" for treating severe HTG and the later "CV Indication" for reducing cardiovascular risk in patients with HTG. Appx514 (FAC, ¶56) (citing Appx635-648 (FAC, Ex. D)).

After the second approval, Amarin removed language from its label that indicated Vascepa® had not been approved for cardiovascular risk reduction, i.e., the "CV Limitation of Use." Appx514-517 (FAC, ¶¶60-63).

The FDA's decision to approve Vascepa® for cardiovascular risk reduction was considered a "major milestone in cardiovascular prevention." Appx518 (FAC, ¶66) (citing Appx685-689 (FAC, Ex. I)). Once Vascepa® received approval for cardiovascular risk reduction and the related limitation was removed from the Vascepa® label, "healthcare providers rapidly associated administration of [E-EPA] together with a statin as a method for reducing risk of cardiovascular events in patients with baseline triglycerides ≥ 150 mg/dL," i.e., in patients with HTG. Appx519 (FAC, ¶67).

Based on work performed in connection with the REDUCE-IT trial, Amarin obtained U.S. Patent No. 10,568,861, which is one of the two patents at issue in this appeal and, unlike the previously litigated severe HTG patents, is directed to cardiovascular risk reduction. *See* Appx107 ('861 patent, 1:49-51); Appx128 ('861 patent, 43:7-14). Claims 1 and 2 of the '861 patent cover methods for reducing the risk of cardiovascular death in patients with established cardiovascular disease by administering Vascepa:

> 1. A method of reducing risk of cardiovascular death in a subject with established cardiovascular disease, the method comprising administering to said subject about 4 g

> of ethyl icosapentate per day for a period effective to reduce risk of cardiovascular death in the subject.
>
> 2. The method of claim 1, wherein the subject has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL and a fasting baseline LDL-C level of about 40 mg/dL to about 100 mg/dL.

Appx129. On March 20, 2020, Amarin timely submitted information regarding the '861 patent to the FDA for listing in the Orange Book as covering methods of using Vascepa® to reduce cardiovascular risk. Appx520 (FAC, ¶77).

4. Mochida's prior foundational work and patent

Amarin's clinical trials related to Vascepa® were preceded by other work done by Mochida, a Japanese pharmaceutical manufacturer that later became Amarin's licensing partner, in the late 1990s and early 2000s. Appx510 (FAC, ¶36). Mochida established through its own cardiovascular outcomes trial that 1.8 grams per day of E-EPA, i.e., the same active ingredient as in Vascepa®, suppressed certain cardiovascular risk in patients with high cholesterol, i.e., hypercholesterolemic patients. Appx510-511 (FAC, ¶36); Appx616 (FAC, Ex. B at Procedures). A statistical analysis of Mochida's trial results was later conducted to assess the effect of EPA on a Japanese patient population with a particular profile of risk factors for coronary artery disease, and its results were published in a 2008 article by Saito *et al.*, titled, "Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: Sub-analysis of primary prevention cases from

the Japan EPA Lipid Intervention Study (JELIS)," 200 Atherosclerosis 135-400 (2008) (hereafter the "Saito article"). Appx511 (FAC, ¶¶37-40) (citing Appx615-620 (FAC, Ex. B)).

U.S. Patent No. 9,700,537, the other patent at issue in this appeal, is based on work performed in connection with the Saito article. The '537 patent describes a method of reducing the risk of a cardiovascular event by administering EPA, with the active ingredient E-EPA, in combination with a statin to a patient with high cholesterol, elevated triglycerides, and reduced HDL-C (good cholesterol). Appx1416 (R&R, 4); Appx40 ('537 patent, 3:14-40). Claim 1 states:

> 1. A method of reducing occurrence of a cardiovascular event in a hypercholesterolemia patient consisting of:
> identifying a patient having triglycerides (TG) of at least 150 mg/DL and HDL-C of less than 40 mg/dL in a blood sample taken from the patient as a risk factor of a cardiovascular event, wherein the patient has not previously had a cardiovascular event, and administering ethyl icosapentate in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor,
> wherein said 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitor is administered to the patient at least one of before, during and after administering the ethyl icosapentate; and
> wherein the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor is selected from the group consisting of pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin, pitavastatin, rosuvastatin, and salts thereof, and
> wherein daily dose of the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor are 5 to 60 mg for pravastatin, 2.5 to 60 mg for simvastatin, 10 to 180 mg

> for fluvastatin sodium, 5 to 120 mg for atorvastatin calcium hydrate, 0.5 to 12 mg for pitavastatin calcium, 1.25 to 60 mg for rosuvastatin calcium, 5 to 160 mg for lovastatin, and 0.075 to 0.9 mg for cerivastatin sodium.

Appx46. The '537 patent is assigned to Mochida, and Amarin holds the exclusive license to it. Appx512 (FAC, ¶¶42-43). On January 9, 2020, Amarin timely submitted information regarding the '537 patent to the FDA for listing in the Orange Book as covering methods of using Vascepa® to reduce cardiovascular risk. Appx519 (FAC, ¶71).[2]

The '537 and '861 patents cover the CV Indication for Vascepa®, and that CV Indication currently accounts for more than 90% of Vascepa® sales. Appx923-925 (Amarin's letter to its payer community after Hikma's generic launch); Appx540 (FAC, ¶152).

B. Hikma launched generic Vascepa®, describing it on its website, in press releases, and with a supposedly "skinny" label

1. Hikma submitted a Section viii statement to obtain FDA approval to sell generic Vascepa® solely to treat severe hypertriglyceridemia

On September 21, 2016, Hikma (through its predecessor) submitted an abbreviated new drug application for a generic version of Vascepa®. Appx525 (FAC, ¶99). While Hikma's application was pending, the '537 and '861 patents issued. *See*

[2] The record below also involved U.S. Patent No. 8,642,077, but the parties resolved their dispute regarding that patent, and it is not relevant to this appeal.

Appx36 (’537 patent); Appx77 (’861 patent); Appx613 (FAC, Ex. A). Because Amarin listed both the ’537 and ’861 patents in the Orange Book before Hikma’s generic version of Vascepa® was approved, Hikma was required to provide to the FDA either patent certifications under Section vii or a statement under Section viii. *See* 21 U.S.C. § 355(j)(2)(A)(vii-viii); 21 C.F.R. § 314.94(a)(12); Appx526 (FAC, ¶ 102). A “Section viii statement” (submitted under 21 U.S.C. § 355(j)(2)(A)(viii)), is filed when a generic applicant seeks FDA approval to label its drug only for uses *not* covered by method-of-use patents, like those at issue here. Appx524-525 (FAC, ¶ 95). Because the resulting generic’s label would include less than the full label by virtue of the excluded patented indications, it is common to refer to a generic under a Section viii statement as a “skinny label” drug. *See GlaxoSmithKline LLC v. Teva Pharms. USA, Inc.*, 7 F.4th 1320, 1328 (Fed. Cir. 2021) (per curiam) (noting that Teva’s label prepared under Section viii was “a so-called ‘skinny label.’”). In this case, Hikma submitted a Section viii statement to the FDA with respect to the ’537 and ’861 patents, seeking FDA approval for only the severe HTG indication. Appx526 (FAC, ¶ 104).

After the severe HTG patents were invalidated in the Nevada action, and based on its Section viii statement, the FDA granted final approval for Hikma’s ANDA on May 21, 2020. Appx506 (FAC, ¶ 11); Appx613 (FAC, Ex. A). Hikma

launched its generic version of Vascepa® in the United States in November 2020. Appx506 (FAC, ¶13) (citing Appx715-717 (FAC, Ex. N)).

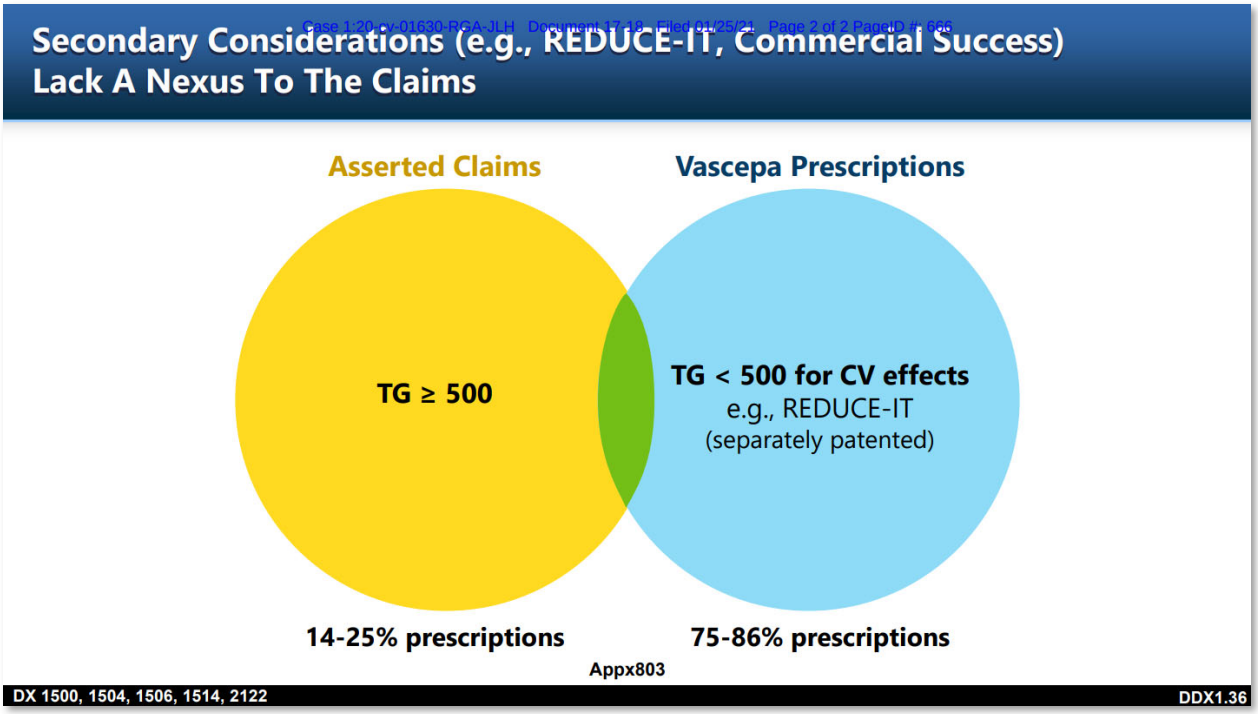
2. Hikma's website associated its generic version of Vascepa® with a method of use beyond its approved use

When Hikma launched its generic version of Vascepa®, with its approved indication limited to treating severe HTG, Hikma's website announced that its product was in the Therapeutic Category of "Hypertriglyceridemia." Appx532 (FAC ¶125) (citing Appx820 (FAC, Ex. T (Hikma's website))). Treating patients having *severe* HTG—the approved indication—means treating patients with triglyceride levels of at least 500 mg/dL. But "hypertriglyceridemia," i.e., HTG, as opposed to severe HTG, generally refers to patients having triglycerides of over 150 mg/dL who are at increased cardiovascular risk—the very patients studied in the REDUCE-IT trial for cardiovascular risk reduction. Hikma's website thus promoted its generic E-EPA capsules as therapeutically equivalent for a use beyond treating patients with severe HTG. Appx532-533 (FAC, ¶126).[3] Hikma has not explained why it declined to accurately describe the therapeutic category as Severe Hypertriglyceridemia.

[3] Hikma knew that broader use would include the patented indication. In the Nevada trial based on Amarin's severe HTG patents, Hikma acknowledged that there are 'several reasons why a physician might prescribe Vascepa (or the Hikma Defendants' ANDA Products) … other than to treat severe hypertriglyceridemia,' including to reduce cardiovascular risk." Appx529 (FAC, ¶110) (citing Appx845-847 (FAC, Ex. W, ¶116)).

3. Hikma issued press releases, encouraging readers to prescribe generic Vascepa® for more than treating patients with severe hypertriglyceridemia

Beyond its website, Hikma also issued pre-launch press releases that carefully conveyed to readers that Hikma's product should be used for all uses for which Vascepa® was approved. First, the press releases indicated that Vascepa® is indicated only "in part" to treat patients with severe HTG. Appx709; Appx712. Hikma's press releases went further and identified its product as "Hikma's generic version" of Vascepa® without any qualification and in an attempt to equate Hikma's approval to the two Vascepa® indications. Appx709; Appx712. In fact, the later press release announced that Hikma had "received FDA approval of the product" without acknowledging that the approval was only for the severe HTG indication. Appx712. Taken together, Hikma made clear that Vascepa® was indicated for more than one use and then identified its own product as a generic version of Vascepa®. In describing its "generic version of Vascepa," both press releases further touted the value of *all* domestic Vascepa® sales, *id.*, even though Hikma knew more than 75% of sales were for the (patent-protected) CV Indication. Appx529 (FAC, ¶¶112-113); Appx531 (FAC, ¶¶119-120); Appx846 (¶115 (Hikma's proposed findings of fact from the Nevada trial)); Appx803 (FAC, Ex. Q). Hikma illustrated the lopsided sales in favor of the "separately patented" CV Indication during the Nevada trial in one of its demonstratives to downplay the commercial success of the SH Indication:



Appx803 (FAC, Ex. Q).

Amarin asserted those pre-launch press releases as evidence supporting its allegations that Hikma developed its product based on market assumptions that included the universe of Vascepa® sales, not just sales related to sever HTG treatment. Appx528 (FAC, ¶109). Importantly, Amarin alleged that Hikma's press releases "communicate[d] to and instruct[ed] healthcare providers and patients that Hikma's 'generic version' of VASCEPA® should be used for all the same indications as VASCEPA®, including to reduce the risk of [cardiovascular] events per the CV Indication awarded to VASCEPA®, and thus promote[d] and encourage[d] that use." Appx530 (FAC, ¶115); Appx531 (FAC, ¶122). It was only after its launch that Hikma finally noted in a press release that its product had limited approval,

Appx715, but by that time Hikma had already primed the market with its earlier press releases.

4. Hikma's "skinny" label teaches the claimed limitations and omits the prior limitation of use excluding the cardiovascular risk indication

Hikma's label (Appx693-707) includes information that Amarin asserted would encourage a healthcare provider to prescribe its generic product for the patented and non-approved CV Indication. For example, the REDUCE-IT study—which was relevant solely to the CV Indication—is described in section 5.1 of Hikma's label. Appx696. Co-administering with a statin (part of the CV Indication) is discussed in sections 12.3 and 14.2. Appx701-702. And Hikma itself recognized that the patient population for the severe HTG indication overlaps in part with the patient population for the cardiovascular risk indication. Appx803 (FAC, Ex. Q). Further, Hikma's label identifies potential side effects, stating in part that people who have cardiovascular disease or diabetes with a risk factor for cardiovascular disease may experience heart rhythm problems when they take Hikma's product:

> **Heart rhythm problems (atrial fibrillation and atrial flutter).** Heart rhythm problems which can be serious and cause hospitalization have happened in people who take icosapent ethyl, especially in people who have heart (cardiovascular) disease or diabetes with a risk factor for heart (cardiovascular) disease, or who have had heart rhythm problems in the past.

Appx704-705 (FAC, Ex. K).

Hikma's label makes clear that: "Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet." Appx535 (FAC, ¶132); Appx705. One of Hikma's physician experts in the Nevada trial pointed to that language when explaining that "most often we use this medication for reasons other than the [severe HTG clinical trial] data, and in the patient information section it specifically tells the patients that we would potentially do that." Appx535 (FAC, ¶132) (citing Appx849-850 (FAC, Ex. X at 617)). In other words, Hikma's physician understood that the label tells readers that Hikma's product will be prescribed for reasons other than treating patients with severe HTG.

Beyond including information relevant to the CV Indication, Hikma removed a relevant Limitation of Use from its label. When Hikma submitted its ANDA (September 21, 2016), Vascepa® was approved only for the severe HTG indication, and the Vascepa® label included a statement in its Limitation of Use section, which said: "The effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined." Appx514-515 (FAC, ¶60) (citing Appx650-661 (FAC, Ex. E); Appx663-672 (FAC, Ex. F)). Hikma's proposed label thus included the same Limitation of Use.

The FDA's approval of Vascepa® for the cardiovascular indication allowed *Amarin* to add a cardiovascular risk reduction indication to, and remove the cardiovascular Limitation of Use from, the Vascepa® label. However, *Hikma* also

removed the cardiovascular Limitation of Use from its proposed label and did so with knowledge of the '537 and '861 patents. Appx528 (FAC, ¶108). When Hikma launched its product, its label did not include any cardiovascular Limitation of Use. *See* Appx526 (FAC, ¶107) (citing Appx694-707 (FAC, Ex. K)). Amarin alleged that Hikma removed that Limitation of Use "so that healthcare providers and patients would believe that Hikma's generic [E-EPA] capsules could be and should be used just like VASCEPA®, including to reduce the risk of cardiovascular events per the CV Indication awarded to VASCEPA®." Appx528 (FAC, ¶108). That allegation is well founded because the market understands what the presence of the cardiovascular Limitation of Use implies because another similar well-known drug, Lovaza®, which contains EPA and lowers triglyceride levels, includes the same limitation and has not been shown to be effective for reducing cardiovascular risk. Appx516 (FAC, ¶61) (citing Appx807-818 (FAC, Ex. S)); Appx518 (FAC, ¶64).

C. The district court proceeding

1. Amarin sued Hikma for inducing infringement

On November 30, 2020, Amarin sued Hikma for inducing infringement of the '861 and '537 patents ("the asserted patents"), Appx159-166 (Compl., ¶¶120-143), and on January 25, 2021, Amarin filed its First Amended Complaint ("FAC"), Appx504-557. Amarin alleged that the combination of Hikma's label, its press releases, and its website encouraged healthcare providers to: (i) associate Hikma's

generic with the patented use of Vascepa® known to the market; and (ii) administer Hikma's generic version of Vascepa® to patients with non-severe HTG in order to reduce cardiovascular risk. Appx533 (FAC, ¶¶ 127-128).[4]

2. Hikma moved to dismiss under Rule 12(b)(6)

Hikma moved to dismiss the inducement claims under Federal Rule of Civil Procedure 12(b)(6) for failure to state a claim. Appx941-968 (MTD). Hikma did *not* dispute that Amarin sufficiently alleged that healthcare providers had directly infringed the '537 and '861 patents or that Hikma knew about the asserted patents and the direct infringement. And, Hikma admitted that the district court could consider Amarin's allegations about Hikma's website, press releases, and label. Appx950 (MTD, 3) ("Now that Hikma recently launched its product, Amarin can rely on information outside of the labeling to prove inducement."). Rather, Hikma's motion was limited to arguing that Amarin did not plausibly allege that Hikma took "active steps" to encourage that infringement, despite Amarin's allegations regarding Hikma's website and press releases in addition to its label. Appx945 (MTD, ToC); Appx1011 (Reply, 10).

[4] Amarin amended its complaint once to add allegations, mostly related to Amarin's decision to add another defendant: Health Net, LLC. Appx558. Health Net separately moved to dismiss the first amended complaint, and Health Net's motion was denied. Amarin and Health Net subsequently resolved their dispute, so Health Net is not part of or related to this appeal.

3. The magistrate judge recommended denying Hikma's motion to dismiss

The magistrate judge recommended denying Hikma's motion to dismiss. Appx503; Appx1430 (R&R, 18). Recognizing that it could not "make factual findings about what Hikma's label and advertisements communicate to physicians," Appx1414 (R&R, 2), the magistrate judge explained why Amarin's allegations could not be resolved on the pleadings. The impact of Hikma's actions on healthcare providers raised a factual dispute that could plausibly be resolved in Amarin's favor:

> Hikma urges the Court to resolve this case at the pleadings stage, pointing out that the contents of its label and public statements are undisputed. *But there is a real dispute about what those contents communicate to others*, and I do not think it is appropriate to resolve it on a motion to dismiss. Stated another way, at this stage of the case, I am not prepared to say that Hikma's label and public statements—as a matter of law—could never amount to instruction and encouragement to infringe the asserted patents.

Appx1427 (R&R, 15) (emphasis added).

The magistrate judge agreed with Hikma that it had no duty to actively discourage infringement, and further agreed that Hikma's mere knowledge of direct infringement would be insufficient on its own to state a claim. Appx1426 (R&R, 14). "But [Hikma] cannot present information in a way that encourages infringement." Appx1426 (R&R, 14). Amarin plausibly alleged that is exactly what Hikma did. The magistrate judge recognized that Amarin's various allegations

should be considered together, not individually, and viewed in a light most favorable to Amarin. *See* Appx1424-1425 (R&R, 12-13). As the magistrate judge explained, "[t]he assessment of whether a complaint plausibly alleges inducement in a pharmaceutical case is thus no different than the analysis in any other case." Appx1423 (R&R, 11).

4. The district court granted Hikma's motion

The district court overruled the magistrate judge's recommendation and granted Hikma's motion to dismiss. Appx2. Beginning with Hikma's label, the district court explained that it could find no instruction "as to CV risk reduction." Appx6. In analyzing Hikma's label, the district court focused on "CV risk reduction," and not the claimed patient population. In so doing, the "side effect" language was "hardly instruction or encouragement" to use Hikma's generic drug to reduce cardiovascular risk. Appx6. The district court opinion did not discuss whether the "side effect" language would be understood by healthcare providers as encouraging them to prescribe Hikma's generic drug to the patient population claimed in the '537 or '861 patents. And the district court found that Hikma had no duty to discourage the patented use. Appx7. Even if removing the Limitation of Use communicated to the public that Hikma's generic drug could be used to reduce cardiovascular risk, the district court reasoned that healthcare providers would

understand that as Hikma "merely describing" an infringing mode, not encouraging it. Appx7.

The district court then set the label aside to separately analyze the non-label allegations: "Since I find that the label does not instruct CV risk reduction, the question is whether Hikma's public statements, including press releases and Hikma's website, induce infringement." *Id.*

As to Hikma's pre-launch press releases, the district court concluded that advertising its product as the "generic equivalent" of Vascepa® did not expose Hikma to liability under *GlaxoSmithKline* and citing sales figures for infringing uses goes to Hikma's "intent to induce" but does not count as an inducing act. Appx8.

Turning to Hikma's website that advertised Hikma's product in the "hypertriglyceridemia" therapeutic category, the district court acknowledged that "Amarin has pled that the category 'hypertriglyceridemia' includes infringing uses." Appx8. Again, isolating the analysis, the district court reasoned "[t]he question is whether this is enough, without a label or other public statements instructing as to infringing use, to induce infringement," and decided the answer was "no." Appx8.

To justify its conclusion, the district court compared the facts here to the facts in *GlaxoSmithKline* (finding infringement) and *Grunenthal GMBH v. Alkem Labs. Ltd.*, 919 F.3d 1333 (Fed. Cir. 2019) (finding no infringement), and concluded this case was more like *Grunenthal* than *GlaxoSmithKline*. Appx8-9. The district court

attempted to distinguish Teva's press releases in *GlaxoSmithKline*, which described the Teva product as a generic "cardiovascular agent," a category that included infringing and non-infringing uses, from Hikma's website. Appx9. The district court found Hikma's website was less like the press releases in *GlaxoSmithKline* and more like the label at issue in *Grunenthal*, where the label included a broader, non-patented category, which by definition covered a narrower, patented use. Appx9. In *Grunenthal*, this Court found that listing the non-patented, broader category on the label was not a specific encouragement to use the drug for the narrower, patented purpose. *Grunenthal*, 919 F.3d at 1339; *see* Appx9. The district court did not comment on the distinction between *Grunenthal* and this case, namely, that the relationship between the non-patented use and patented use is reversed: the non-patented use here (i.e., the severe HTG indication) is *narrower* than the patented use (i.e., the cardiovascular risk reduction indication for general HTG). Hikma's website did not list a non-patented use that included a narrower patented use like the *Grunenthal* label; instead, Hikma listed a broader general HTG therapeutic category where the majority of prescriptions would be for the patented use to reduce cardiovascular risk. *See* Appx820 (FAC, Ex. T); Appx529 (FAC, ¶¶112-113); Appx531 (FAC, ¶¶119-120).

The district court concluded that Amarin "failed to plead inducement based on Hikma's label or public statements" and granted Hikma's motion to dismiss the first amended complaint. Appx9.

SUMMARY OF ARGUMENT

This case involves Hikma's so called skinny-label generic version of Amarin's breakthrough Vascepa® medication, but the evidence in this case goes beyond the label, skinny or not. This is a pleadings standard case. Yes, Amarin alleged that Hikma's skinny label was not skinny enough, i.e., that it covered patented methods of treatment. But Amarin alleged more than that.

Amarin alleged that Hikma, knowing that the "vast majority" of Vascepa® prescriptions were for the patented breakthrough cardiovascular risk reduction treatment, undertook a series of communications with the market with the intent that its generic be used to replace Vascepa® for the patented use. Hikma broadcast a broader therapeutic category (hypertriglyceridemia) than it had approval for (severe hypertriglyceridemia) and then emphasized the generic equivalency of its product with Vascepa®—most often used for cardiovascular risk reduction—through Hikma's website, multiple press releases, and the language of Hikma's label. It is more than plausible that Hikma intended these active steps to influence prescribing physicians to replace Vascepa® with its generic for the patented use. That was

enough to satisfy the pleading requirements and survive the motion to dismiss. Holding otherwise resulted in multiple errors.

The district court erred by: (1) weighing Amarin's allegations separately and in isolation against the plausibility pleading standard rather than considering whether, as Amarin pled, Hikma's conduct as a whole induced infringement; (2) making implicit factual findings on the key question of what Hikma's conduct communicated to prescribing physicians; and (3) misapplying skinny-label precedent. Those errors effectively and improperly elevated the pleading standard to deprive Amarin of its right to pursue a more than plausible claim for induced infringement. Reversal and remand is appropriate.

ARGUMENT

I. Standard of review

This Court reviews motions to dismiss for failure to state a claim under the law of the regional circuit. *Visual Memory LLC v. NVIDIA Corp.*, 867 F.3d 1253, 1257 (Fed. Cir. 2017). The Third Circuit reviews the district court's grant of such a motion de novo. *Ballentine v. United States*, 486 F.3d 806, 808 (3d Cir. 2007).

II. Amarin satisfied the pleading standard by pleading plausible infringement by Hikma

The requirement to state a plausible claim for relief at the pleading stage is not demanding. The specific claim here, induced infringement, requires encouragement or promotion of an infringing use. Amarin pled multiple facts that

together demonstrated how Hikma encouraged or promoted prescribing physicians to replace Amarin's Vascepa® with Hikma's generic for the patented use of reducing cardiovascular risk in patients with elevated triglyceride levels.

A. Surviving a motion to dismiss requires pleading facts sufficient to state a plausible claim for relief

"To survive a motion to dismiss, a complaint must contain sufficient factual matter, accepted as true, to 'state a claim to relief that is plausible on its face.'" *Ashcroft v. Iqbal,* 556 U.S. 662, 678 (2009) (quoting *Bell Atl. Corp. v. Twombly,* 550 U.S. 544, 570 (2007)). Only "a short and plain statement of the claim showing that the pleader is entitled to relief" is required. Fed. R. Civ. P. 8(a)(2). Factual allegations are reviewed "on the assumption that all the allegations in the complaint are true (even if doubtful in fact)." *Twombly,* 550 U.S. at 555. The allegations do not need to be detailed. *Id.* Instead, "[f]actual allegations must be enough to raise a right to relief above the speculative level," as opposed to allegations that provide a "formulaic recitation" of the claim elements. *Id*.

This was not a case where Amarin merely speculated about what doctors might do. Instead, Amarin set forth allegations of how Hikma used multiple communications on its website, press releases, and label together to encourage using its generic as a replacement for Vascepa® for the patented use. Those allegations easily exceeded mere speculation.

A claim is plausible when the complaint contains "factual content that allows the court to draw the reasonable inference that the defendant is liable for the misconduct alleged." *Iqbal,* 556 U.S. at 678 (citing *Twombly*, 550 U.S. at 556). The plausibility requirement is not a "probability requirement." *Twombly,* 550 U.S. at 556. "[I]t simply calls for enough fact to raise a reasonable expectation that discovery will reveal evidence" showing the alleged misconduct. *Id.* "[A] well-pleaded complaint may proceed even if it strikes a savvy judge that actual proof of those facts is improbable, and 'that a recovery is very remote and unlikely.'" *Id.* (quoting *Scheuer v. Rhodes*, 416 U.S. 232, 236 (1974)). "The issue is not whether a plaintiff will ultimately prevail but whether the claimant is entitled to offer evidence to support the claims." *In re Burlington Coat Factory Sec. Litig.*, 114 F.3d 1410, 1420 (3d Cir. 1997).

Amarin alleged facts showing how Hikma's multiple communications plausibly encouraged infringement. Those allegations highlighted a key factual dispute over how prescribing physicians would understand Hikma's multiple communications—a dispute that would be informed by discovery and expert testimony. But even without that discovery and testimony—prematurely cutoff by the district court—Amarin's alleged facts were enough to create a "reasonable inference," *Iqbal,* 556 U.S. at 678, that Hikma's multiple communications encouraged physicians to use Hikma's generic for the patented use.

B. Inducement requires showing direct infringement and actions taken with the intent to cause infringing conduct

Section 271(b) of Title 35 provides that "[w]hoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). To state a claim of induced infringement under § 271(b), the complaint must plausibly allege that: (1) there has been direct infringement; (2) the defendant knowingly induced infringement; and (3) the defendant possessed the intent to encourage another's infringement. *MEMC Elec. Materials, Inc. v. Mitsubishi Materials Silicon Corp.*, 420 F.3d 1369, 1378 (Fed. Cir. 2005).

A generic manufacturer can be liable for inducing infringement even when it has attempted to "carve out" the patented indications with a skinny label. *GlaxoSmithKline*, 7 F.4th at 1338; *see AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1056-61 (Fed. Cir. 2010) (affirming grant of preliminary injunction against generic manufacturer for inducing infringement of the patented use even though generic product was approved for the non-patented use). Thus, in considering a motion to dismiss in a pharmaceutical case like this, the court must still determine whether the complaint plausibly alleges inducement.

The inducement inquiry considers whether the complaint plausibly alleges that the generic manufacturer "offer[ed] a product with the object of promoting its use to infringe, as shown by clear expression or other affirmative steps taken to foster infringement." *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1305-06 (Fed. Cir.

2006) (en banc in relevant part). And the Supreme Court has held that advertising or instructing an infringing use is evidence of active steps that both encourage infringement and demonstrate the affirmative intent to induce infringement. *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 936 (2005); *see Takeda Pharms. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 630-31 (Fed. Cir. 2015) ("Inducement can be found where there is '[e]vidence of active steps taken to encourage direct infringement,' which can in turn be found in 'advertising an infringing use or instructing how to engage in an infringing use.'") (quoting *Grokster*, 545 U.S. at 936). Rather than alleging a defendant's "mere knowledge" that its product could be used to infringe, *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003), allegations should plausibly suggest "culpable conduct, directed to encouraging another's infringement." *DSU Med.*, 471 F.3d at 1306.

C. Taking the allegations together, Amarin's claim against Hikma is plausible, and discovery is likely to further support Amarin's case

Under the plausibility pleading standard, Amarin was not required to prove its inducement claim to survive the motion to dismiss. Amarin was only required to plead a plausible claim for relief. Amarin did so.

Because Hikma did not dispute either that its generic form of Vascepa® was being used to reduce cardiovascular risk or that such use directly infringed the asserted patents, the issue before the district court was whether Amarin had pled

facts plausibly showing Hikma acted to induce that infringement. *MEMC Elec. Materials*, 420 F.3d at 1378. Amarin pled multiple facts that plausibly demonstrated how Hikma's cumulative actions were taken with the intent to encourage and promote infringement. *Grokster*, 545 U.S. at 936; *DSU Med.*, 471 F.3d at 1305-06.

First, on its website, Hikma described its generic as being therapeutically equivalent to Vascepa® in a broad indication category of "hypertriglyceridemia," i.e., HTG generally. Appx532 (FAC ¶125) (citing Appx820 (FAC, Ex. T (Hikma's website))). That broad category exceeds Hikma's authorized use to treat *severe* HTG in patients with triglyceride levels above 500 mg/dL because it includes the unauthorized, patented use to reduce cardiovascular risk in patients with triglyceride levels above 150 mg/dL, i.e., patients who suffer from HTG (where the primary concern is cardiovascular risk reduction) but not *severe* HTG (where the primary concern is pancreatitis). Appx532-533 (FAC, ¶¶125, 126). Thus, Hikma communicated to the market that its generic was equivalent to Vascepa® for the patented use.

Second, Hikma's marketing campaign included press releases that communicated to the market that Hikma's generic was equivalent to Vascepa® without limitation on use. At the close of the Nevada trial over the severe HTG patents, Hikma announced that it was seeking approval for "its generic version of Vascepa®." Appx709-710. That press release did not divulge that Hikma was

seeking approval only for a particular use of Vascepa®. To the contrary, Hikma identified that particular use as only among the indications for which Vascepa® was approved. *Id.* (describing Vascepa® as "a prescription medicine that is indicated, in part, … to reduce triglyceride levels in adult patients with severe … hypertriglyceridemia."). When Hikma received approval, it announced that the FDA had approved "its [E-EPA] Capsules, 1 gm, *the generic equivalent to Vascepa*." Appx613 (emphasis added). There is no equivocation in that press release, which speaks in terms of the approval of a drug, not a use, and fails to acknowledge that the FDA had approved its generic only for a single indication. And then when Hikma won on appeal following the Nevada trial, it again announced it had received approval for its generic version of Vascepa® without mentioning that approval was limited to the less common indication. Appx712-713. Beyond its silence about the nature of its limited approval, Hikma added that "US sales of Vascepa were approximately $1.1 billion in the 12 months ending in July 2020." *Id.* That figure was extraordinarily misleading in context because, as discussed below, Hikma was aware that those sales were almost all for the use of Vascepa® to treat cardiovascular risk in patients with HTG, a use for which Hikma could not legally compete.

Third, in making these associations, Hikma was aware that the vast majority of prescriptions for Vascepa® were for reducing cardiovascular risk and not for treating severe HTG—the only indication for which its generic is approved. In the

earlier Nevada trial involving the severe HTG patents, Hikma made such an admission even before the FDA had given Amarin approval to market Vascepa® for that use. *See, e.g.*, Appx846 ¶115 (Hikma's proposed finding of fact that "the vast majority of Vascepa prescriptions—over 75%—have been for . . . treating patients with triglycerides below 500 mg/dL."); Appx847 ¶440 (Hikma's proposed finding of fact that "the 'vast majority' of Vascepa® prescriptions are off-label, to patients with triglyceride levels lower than 500 mg/dl"); Appx528-529, Appx535 (FAC, ¶¶110, 132). Following FDA approval of treating cardiovascular risk, that second indication accounted for more than 90% of uses of Vascepa®. Appx923-925 (Amarin's letter to its payer community after Hikma's generic launch); Appx540 (FAC, ¶152). And Hikma knew that doctors had "rapidly associated" Vascepa® with treatment of patients with HTG to reduce cardiovascular risk. Appx519 (FAC, ¶67). Thus, Hikma's communications, which failed to mention that limited nature of the FDA's approval, relied on that association between Vascepa® and the patented use for which Hikma's generic equivalent was not authorized.

Fourth, while Hikma removed some instructions for the unauthorized use from its supposedly skinny label, it maintained in the clinical studies section descriptions of statin-treated patients with the same cardiovascular event history and lipid levels covered by the patented methods. Appx534-536 (FAC, ¶¶130-131, 134); Appx702 (FAC, Ex. K §14.2). And the well-known REDUCE-IT trial related to

cardiovascular risk reduction was described on the label too. Appx696 (FAC, Ex. K § 5.1).

Fifth, Hikma omitted the CV Limitation of Use from its label, a limitation that appears on the only other medication on the market that contains E-EPA and is indicated for lowering triglyceride levels, Lovaza®. Appx514-517 (FAC, ¶¶ 60-61); Appx527-528 (FAC, ¶108). The absence of this limitation, present on the Lovaza® label and understood by physicians, was another way the label communicated to the market that Hikma's generic could be used for the unauthorized, patented cardiovascular risk reduction indication. Appx535-536 (FAC, ¶ 133).

Sixth, Hikma's label identifies a patient population with triglyceride levels above 150 mg/dL that overlaps with patients being treated for cardiovascular risk. Appx696 (FAC, Ex. K § 1).

Far from a purely speculative or formulaic recitation of claim elements, Amarin's complaint presents a clear theory of how Hikma's communications plausibly encouraged or promoted the patented and unapproved use of Hikma's generic version of Vascepa® to reduce cardiovascular risk in patients with elevated triglyceride levels. As the magistrate judge recognized, those factually supported allegations cleared the low pleading bar and prevented dismissal. But rather than reviewing the pled facts and actions together against the low bar of plausibility, the district court considered each fact in isolation. Even if no pled fact by itself could

support the reasonable inference that Hikma has induced infringement, that is irrelevant. Amarin pled that Hikma's multiple communications together encouraged and promoted doctors' use of Hikma's generic for the patented and unapproved use. Those multiple pled facts cleared the low bar for plausibility.

III. The district court erred by weighing the pled facts piecemeal against the plausibility pleading standard

By considering each factual allegation in isolation, the district court transformed the inquiry from one requiring "a short and plain statement of the claim showing that the pleader is entitled to relief," Fed. R. Civ. P. 8(a)(2), into an exacting inquiry requiring a single act to sustain the plausibility of Amarin's case. That was error.

The plausibility pleading standard simply requires sufficient factual material to show the claim for relief is plausible on its face, *Iqbal,* 556 U.S. at 678, to "raise a right to relief above the speculative level," *Twombly,* 550 U.S. at 555, and to allow "the court to draw the reasonable inference that the defendant is liable for the misconduct alleged," *Iqbal,* 556 U.S. at 678. It does not require pleading a single fact that by itself establishes the plausibility of a claim because "courts must consider the complaint in its entirety." *Tellabs, Inc. v. Makor Issues & Rts., Ltd.*, 551 U.S. 308, 322 (2007). In the context of the pleading requirement for scienter under the Private Securities Litigation Reform Act, 15 U.S.C. § 78u–4(b)(2), the Supreme Court explained, "The inquiry . . . is whether all of the facts alleged, taken

collectively, give rise to a strong inference of scienter, not whether any individual allegation, scrutinized in isolation, meets that standard." *Id.* at 322-23.

The Third Circuit applied the Supreme Court's rule in the context of a civil rights complaint under 42 U.S.C. § 1983 when it reversed the district court's grant of a motion to dismiss for failure to state a claim. *Kedra v. Schroeter*, 876 F.3d 424, 432 (3d Cir. 2017). In reversing, the court explained that the district court had "done the inverse of what we are required to do at the pleading stage," i.e., "[i]nstead of considering the complaint as a whole, [the district court] consider[ed] 'whether any individual allegation, scrutinized in isolation, meets that standard.'" *Id.* at 444 (quoting *Tellabs*, 551 U.S. at 322-23). Inducement is similarly not limited to a single act. It considers whether the defendant took "active steps . . . to encourage direct infringement." *Grokster*, 545 U.S. at 936. *Cf. In re Bill of Lading Transmission & Processing Sys. Pat. Litig.*, 681 F.3d 1323, 1343 (Fed. Cir. 2012) (finding induced infringement plausible and that the district court erred by concluding otherwise where "the district court analyzed the individual facts in the [] Amended Complaint in isolation and without reference to the background of the invention"). Thus, establishing a plausible inducement claim does not require a single act.

But that is effectively what the district court required here. It decoupled Hikma's actions to determine whether one portion of Hikma's conduct in *isolation* encouraged infringement instead of considering—as Amarin pled—whether

Hikma's *cumulative* conduct encouraged infringement. *See* Appx5 ("These allegations fall into two categories . . . ."); Appx6 ("The bulk of the briefing and oral argument was directed to Hikma's label, and I will address those arguments first."); Appx9 ("Amarin's complaint has failed to plead inducement based on Hikma's label or public statements . . . ."). To be clear, Amarin maintains that Hikma's press releases, its website, and even its label are enough to clear the pleading standard even if considered in isolation. But even if each piece were not enough in isolation, the district court further erred by not considering them collectively.

This error effectively raised the pleading requirement by weighing the allegations separately. The district court isolated the allegations of inducement based on the label from the allegations based on the other public statements. *See* Appx7 ("Since I find that the label does not instruct CV risk reduction, the question is whether Hikma's public statements, including press releases and Hikma's website, induce infringement."). But the district court went even further and isolated the allegations of inducement for portions of Hikma's public statements from other portions. *See* Appx8 ("Amarin has pled that the category 'hypertriglyceridemia' includes infringing uses. The question is whether this is enough, *without a label or other public statements* instructing as to infringing use, to induce infringement.") (emphasis added).

In contrast, the magistrate judge's report and recommendation fairly considered the cumulative allegations as Amarin pled. The magistrate judge noted how Amarin alleged that "portions of Hikma's label, *taken together* with Hikma's public statements, instruct physicians to use Hikma's product in a way that infringes the asserted patents." Appx1424 (R&R, 12) (emphasis added). And rejecting Hikma's arguments about label-only ANDA case law, the magistrate judge explained, "were this an ANDA case, and were [Amarin's] allegations based solely on the label, [Amarin's] inducement theory might lack merit as a matter of law. But this is not an ANDA case, and *[Amarin's] allegations are not based solely on the label*." Appx1426 (R&R, 14) (emphasis added). Thus, the magistrate judge concluded that, when "*taken together* and viewed in the light most favorable to [Amarin]," Amarin's allegations "plausibly suggest . . . that Hikma's *label and public statements* could instruct and/or encourage third parties to use its product for the CV indication, which [Amarin] allege[s] is covered by the asserted patents; and [] that Hikma both knew and intended that third parties would use its product for that purpose." Appx1425 (R&R, 13) (emphasis added).

The report and recommendation properly applied the pleading standard based on what Amarin pled, but the district court did not. This Court should reverse.

IV. The district court erred by resolving the key factual dispute of what Hikma's conduct communicated to the market

Although "the contents of [Hikma's] label and public statements are undisputed," "there is a real dispute about what those contents communicate to others, and I do not think it is appropriate to resolve it on a motion to dismiss." Appx1427 (R&R, 15). With this explanation, the magistrate judge foreshadowed another error by the district court.

Infringement is a fact question. *Grunenthal GMBH v. Alkem Labs. Ltd.*, 919 F.3d 1333, 1339 (Fed. Cir. 2019). In evaluating Amarin's allegations of induced infringement, the key issue is whether Hikma acted to encourage or promote infringement with the intent to cause such infringement. And as the magistrate judge explained, Amarin alleged that "several . . . portions of Hikma's label, taken together with Hikma's public statements, *instruct physicians* to use Hikma's product in a way that infringes the asserted patents." Appx1424 (R&R, 12) (emphasis added). Thus, the key factual dispute was what Hikma's conduct as described in Amarin's factual allegations communicated to prescribing physicians. Although the magistrate judge recognized this key disputed issue—which should have precluded dismissal—the district court ignored it.

Instead of turning to discovery and expert testimony to illuminate how physicians would have understood Hikma's collection of communications through its website, press releases, and label, the district court short-circuited the process and

implicitly decided the key factual dispute on a motion to dismiss. Appx536-537 (FAC, ¶135) ("For all the reasons set forth above, Hikma knows of and specifically intends for healthcare providers to administer its [E-EPA] capsules in the place of VASCEPA® . . . and its labeling and marketing materials promote, encourage, and instruct healthcare providers to practice the methods of the Asserted Patents"). The district court made that inappropriate finding without addressing the question of what was communicated to physicians. *See* Appx6 (determining that Hikma's specific warning about side effects was not "instruction or encouragement"); Appx7 (determining that "the lack of a [cardiovascular] limitation on Hikma's label does not plausibly teach [cardiovascular] risk reduction"); Appx8 (determining that Hikma's broad category listing on its website "does not rise to the level of encouraging, recommending, or promoting taking Hikma's generic for the reduction of [cardiovascular] risk").

GlaxoSmithKline is illustrative. There, the factfinder reviewed exactly what the district court in this case prevented Amarin from presenting—discovery and expert testimony addressing what Hikma's promotional activities and label communicated to prescribing physicians. This Court extensively discussed the expert testimony. *GlaxoSmithKline*, 7 F.4th at 1328-38. In doing so, the Court noted how "GSK's cardiology expert, Dr. McCullough, explained that doctors, the alleged direct infringers, receive information about generic drug products from a variety of

sources, including the drug labels," and "then walked through each element of claim 1 of the [asserted] patent and compared it to Teva's partial label." *Id.* at 1328.

The fact that *GlaxoSmithKline* proceeded through discovery to trial highlights the evidence-depriving error that dismissal in the face of disputed key factual questions caused in this case. And *GlaxoSmithKline* even addressed a parallel error: "Critically, the district court erred by treating this fact question—whether [a certain] indication instructs a physician to prescribe carvedilol for a claimed use—as though it were a legal one for it to decide *de novo*." *Id.* at 1330. Although that case went to trial, the district court usurped the jury's factfinding role on JMOL and "decided the [relevant indication] portion of Teva's label was insufficient to find that the label instructed an infringing use." *Id.* As explained above, the district court in this case made multiple similar *factual* determinations, assessing the weight of the evidence without explicitly considering the key factual question of what that evidence communicated to prescribing physicians.

For "a quintessential fact question," *id.* at 1328, involving "a real dispute about what [Hikma's label and public statements] communicate to others," it was "not . . . appropriate to resolve [] on a motion to dismiss," Appx1427 (R&R, 15). The district court erred when it did so.

V. The district court erred by analogizing the wrong cases

The district court also erred in its misapplication of skinny-label precedent.

A. This case involves evidence showing inducement in addition to the label—it is not a "label only" case

This case is like *GlaxoSmithKline* and *AstraZeneca* in that those cases also included extra-label evidence to show inducement. In *GlaxoSmithKline*, this Court vacated a grant of JMOL for non-infringement and reinstated a jury's verdict finding induced infringement. 7 F.4th at 1323. As discussed above, the Court relied on detailed expert testimony from Dr. McCullough, including the assertion that doctors obtain information about generic medications from drug labels and other sources. *Id.* at 1328-38. The Court found evidence showing that "Teva intended its label to affect physician's prescribing practices," but that was "not the only evidence" because "GSK also presented extensive expert testimony along with Teva's marketing efforts, catalogs, press releases, and testimony from Teva's own witnesses, showing that Teva encouraged carvedilol sales for [congestive heart failure] despite its attempted carve-out." *Id.* at 1335.

Similar to Hikma's website, Appx820, Teva's first press release described its medication as "the AB rated generic equivalent of [GSK]'s Coreg® Tablets" and as "indicated for *treatment of heart failure* and hypertension." *Id.* at 1335-36 (internal quotations omitted) (emphasis in original). The Court noted how Teva's press release used the term "heart failure" in a way that did "not parse between congestive heart failure," i.e., the patented use, and the specific "post-MI LVD" indication that was not patented. *Id.* at 1336. "This [was] not an errant reference to 'heart failure';

it [was] Teva in a press release telling the world that its generic is a substitute for GSK's Coreg® tablets to treat congestive heart failure in the same manner as Coreg® (which is a method that infringed the '000 patent)." *Id.* And the Court noted Dr. McCullough's additional testimony that this press release "indicate[d] physicians should prescribe generic carvedilol for heart failure." *Id.* Teva's second press release "stated that it had received final approval to market its Generic version of [GSK]'s cardiovascular agent Coreg® (Carvedilol) Tablets." *Id.* (internal quotations omitted). Again, Dr. McCullough testified what this communicated to doctors by explaining how Teva's "use of 'cardiovascular agent' indicated to doctors they could use Teva's carvedilol 'for all indications,' including heart failure." *Id.* (internal quotations omitted).

Like the communications in *GlaxoSmithKline* of therapeutic equivalence in a general category of "heart failure" and as a general "cardiovascular agent" that encompassed the patented use to treat congestive heart failure, *id.* at 1335–36, Hikma communicated that its generic medication was equivalent for a general therapeutic category of "hypertriglyceridemia" and listed sales for the whole Vascepa® market to encompass the patented use to reduce cardiovascular risk in patients with HTG. *See* Appx529-533 (FAC, ¶¶111-116, 118-123, 125, 126); Appx612-613 (Hikma's press release on May 22, 2020); Appx708-710 (Hikma's press release on March 31, 2020); Appx711-713 (Hikma's press release on

September 3, 2020). Thus, this case is like *GlaxoSmithKline* in that inducement is shown by more than the label—except the district court erred here by preventing Amarin from developing the case and addressing the key factual dispute.

AstraZeneca is another case with parallels to the dispute here. This Court affirmed the district court's grant of a preliminary injunction that prohibited Apotex's launch of a generic version of AstraZeneca's budesonide medication. 633 F.3d at 1045. The label instructed patients that it was "desirable to downward-titrate to the lowest effective dose once asthma stability is achieved." *Id.* at 1057. AstraZeneca argued this "proposed label would induce consumers to infringe the asserted method claims because the label implicitly instructed users to administer the generic drug once daily," which was covered by the patented method. *Id.* The district court agreed, but it also relied on a letter from the FDA discussing once-daily dosing that demonstrated how Apotex was both communicating about and aware of the infringement problem. *Id.* at 1057, 1059-60. Apotex's awareness of the infringement problem and decision to distribute the generic with the problematic language in the label "formed the basis of the district court's specific intent finding," and the "district court correctly concluded" this was evidence of active steps to encourage infringement. *Id.* at 1059-60. Thus, *AstraZeneca* was another case where inducement, and specifically the necessary intent to induce, was supported by the label plus more. Like in *AstraZeneca*, Amarin alleged that the label itself

demonstrated Hikma's intent to encourage physicians to treat patients with HTG while supporting those label allegations with additional allegations about Hikma's conduct beyond its generic label.

Instead of those cases, the district court here relied on *Grunenthal*, while Hikma cited *HZNP Medicines LLC v. Actavis Laboratories UT, Inc.*, 940 F.3d 680 (Fed. Cir. 2019), and *Takeda*, which relied on *only* the label for inducement. As the magistrate judge explained, "unlike the allegations in this case, the evidence in those cases related solely to the effects of the generic labels." Appx1427.

In *Grunenthal*, this Court affirmed a finding of no induced infringement following a bench trial. 919 F.3d at 1336. There, the brand medication had two indications, the off-patent treatment of "moderate to severe chronic pain in adults," and the patented treatment of "neuropathic pain associated with diabetic peripheral neuropathy (DPN)," which was "a type of [polyneuropathic] pain." *Id.* at 1338. Hikma and another generic manufacturer carved out treatment of DPN. *Id.* at 1339. The inducement inquiry turned on whether Hikma and the other generic had "the specific intent, based on the contents of their proposed labels, to encourage physicians to use their proposed ANDA products to treat polyneuropathic pain." *Id.* The brand owners argued that severe chronic pain, which remained on the generic labels, was broad enough to include the specific patented treatment of polyneuropathic pain. *Id.* This Court disagreed because the off-patent treatment of

severe chronic pain more broadly included other categories: "[E]ven if severe chronic pain includes polyneuropathic pain, it also includes mononeuropathic pain and nociceptive pain." *Id.*

Critically, the brand owners in *Grunenthal* "point[ed] only to the indications of the proposed labels as grounds for inducement." *Id.* at 1340. And the label had effectively carved out the patented indication, which included removing reference to clinical studies for the patented indication: "[I]t is undisputed that neither of the accused ANDA labels list an indication for the management of pain associated with DPN. Nor do they mention any DPN clinical studies, which served as the basis for FDA approval of [the brand medication's] indication for the treatment of neuropathic pain." *Id.* at 1339-40. Thus, *Grunenthal* was a case where inducement was argued based on the label alone, and the generic labels had fully excised the patented indication. In contrast, this case involves allegations of actions beyond the label, as well as allegations that the label was not skinny enough.

In *HZNP*, this Court affirmed a grant of summary judgment finding no induced infringement for patents related to treating osteoarthritis. 940 F.3d at 683. The patented method in *HZNP* required three steps: "(1) apply the inventive formulation, (2) wait for the area to dry, and (3) apply sunscreen, insect repellant, or a second topical medication." *Id.* at 702. But the generic label's instructions only required the first application step with a warning that the area should be allowed to

dry before application of a sunscreen, etc. *Id.* That warning was not enough to show encouragement to infringe because the "evidence, viewed in the light most favorable to [the plaintiff], establishe[d] that some users *might* infringe." *Id.* (emphasis added). The evidence did "not establish that 'the proposed label instruct[ed] users to perform the patented method.'" *Id.* (quoting *AstraZeneca*, 633 F.3d at 1060). *HZNP* like *Grunenthal*, was thus a case that relied on the label alone.

In *Takeda*, Hikma sought approval for a generic medication for the prophylactic treatment of gout but not for the patented "treatment of acute gout flares." 785 F.3d at 630. Hikma's label stated the generic was "indicated for prophylaxis," included a limitation of use that the "safety and effectiveness of [the generic] for acute treatment of gout flares during prophylaxis has not been studied," and included a warning that "[i]f you have a gout flare while taking [the generic], tell your healthcare provider." *Id.* (internal quotations omitted). Takeda argued that the warning would induce infringement because, for a patient using the generic for prophylaxis, "the physician would likely tell the patient to use the [generic] product to treat the acute flare." *Id.* Although Takeda attempted to use evidence beyond the label to demonstrate that the warning would lead physicians to prescribe the generic for the infringing use of treating acute gout flares, the Court found none of the evidence supported inducement. *Id.* at 632.

"[E]ven if we do look outside the label, there is no evidence that the label would necessarily lead doctors who are consulted by patients taking [the generic] to prescribe an off-label use of it to treat acute gout flares." *Id.* The additional evidence did not show additional encouragement or promotion. Instead, the evidence was meant to show how the warning would "inevitably" lead doctors to prescribe the generic for off-label infringing uses, but the evidence failed to show even that. *Id.* *Takeda* was a case that relied on the label alone to show encouragement, and at that, it relied on a warning to see a doctor as the only encouragement to induce infringement. Unlike *Takeda*, this case relies on communications beyond the label.

Like *GlaxoSmithKline* and *AstraZeneca*, this is a case where a label plus more demonstrates inducement. It is not a case like *Grunenthal*, *HZNP*, or *Takeda*, where the generic label alone was used to show an action intended to induce. The district court erred when it relied on *Grunenthal* and distinguished *GlaxoSmithKline*.

B. Previous cases consistently reached a later stage than a motion to dismiss because factual issues are central to inducement

Every leading skinny-label case discussed here and at the district court reached a more advanced posture than a motion to dismiss. *See* Appx1427 (R&R, 15) (magistrate judge noting how "none of those cases [relied upon by Hikma] was resolved at the motion to dismiss stage."). That makes sense. Infringement is a "quintessential fact question," *GlaxoSmithKline*, 7 F.4th at 1328, and induced infringement hinges on factual determinations.

The leading precedent from this Court highlights that the motion to dismiss was an improper vehicle for resolving the key issues in this case—none of the significant cases were appealed from a dismissal on the pleadings. *See GlaxoSmithKline*, 7 F.4th at 1323 (reversing judgment as a matter of law after a jury trial finding infringement); *AstraZeneca*, 633 F.3d at 1045 (affirming grant of preliminary injunction finding likelihood of showing induced infringement); *Grunenthal*, 919 F.3d at 1338 (affirming bench trial finding no infringement); *HZNP*, 940 F.3d at 682, 686 (affirming grant of summary judgment for non-infringement); *Takeda*, 785 F.3d at 627 (affirming denial of preliminary injunction finding no likelihood of showing induced infringement).

To be sure, cases at the preliminary injunction stage are early-stage cases. But a preliminary injunction is a discretionary grant that requires likelihood of success on the merits, *see, e.g.*, *AstraZeneca*, 633 F.3d at 1049, whereas the grant of a motion to dismiss requires the absence of even a plausible claim for relief.

Before the district court, Hikma asserted that there were "many decisions" "even at the pleadings stage" where there was no induced infringement as a matter of law. Appx481-482 n.2 (Hikma's brief in support of its motion to dismiss). Of the ten cases Hikma cited in support, it only described three as involving a dismissal on the pleadings. *Id.* Each of those cases is distinguishable. *Bayer Schering Pharma AG v. Lupin, Ltd.*, was not a skinny-label case—the generic and brand labels were

identical—nor did it involve inducement of an FDA approved use. 676 F.3d 1316, 1321 (Fed. Cir. 2012). *AstraZeneca Pharmaceuticals LP v. Apotex Corp.*, turned on the question of whether infringement under 35 U.S.C. § 271(e)(2)(A) could be based on an ANDA seeking to market a drug that was not patented and for a use that was not patented. 669 F.3d 1370, 1378-79 (Fed. Cir. 2012). And while *Takeda Pharmaceuticals U.S.A., Inc. v. West-Ward Pharmaceutical Corp.*, did involve a dismissal on the pleadings of an inducement claim, that was based on the district court's conclusion that Takeda's allegations were "too conclusory to pass muster." 188 F. Supp. 3d 367, 377 (D. Del. 2016). Significantly, the *Takeda* district court vacated that very dismissal in light of the low pleading standard after Takeda amended its complaint with allegations about specific communications that Takeda argued amounted to active encouragement. *Takeda Pharms. U.S.C., Inv. v. West-Ward Pharm. Corp.*, 2016 WL 723054 at *2 (D. Del. Dec. 14, 2016). Amarin's specific allegations regarding Hikma's website and press releases position this case squarely within the analysis of that later vacatur of the *Takeda* dismissal.

The fact that all the leading skinny-label cases were more advanced than a motion to dismiss confirms that the district erred when it granted the motion to dismiss.

C. This case involves a patented use that is broader than the off-patent use—unlike in *Grunenthal*

Amarin's patented use to reduce cardiovascular risk in patients with HTG covers a broader set of patients than the off-patent use to treat patients with severe HTG. In other words, more patients suffer from elevated triglyceride levels above 150 mg/dL, i.e., patients with HTG, than the subset with levels above 500 mg/dL, i.e., patients with *severe* HTG. The district court analogized to *Grunenthal* and got this point exactly backwards. Vascepa®'s additional patented indication is not simply a subset of its original indication—it is a different use of the drug to treat a broader patient population for which there was a different clinical concern.

Describing the distinct situation in *Grunenthal*, the district court here explained how "a label indicated for '[m]oderate to severe chronic pain,' which included both infringing and non-infringing uses, did 'not specifically encourage use' of the generic for the patented treatment." Appx9 (quoting *Grunenthal,* 919 F.3d at 1339) (modification in original). And the district court concluded, "[t]his case is more like *Grunenthal,* where the broader category simply includes both infringing and non-infringing uses, without 'specifically encourage[ing]' the use of the generic for the non-infringing uses." Appx9 (quoting *Grunenthal,* 919 F.3d at 1339) (modification in original). But the "broader category" in *Grunenthal* was the off-patent treatment of "moderate to severe chronic pain in adults." *Grunenthal*, 919 F.3d at 1338. That method was directed to a broader group of patients than those

with "neuropathic pain associated with diabetic peripheral neuropathy (DPN)," which was "a type of polyneuropathic pain." *Id*. This Court rejected the argument that the generic label for the broader, off-patent use induced the specific, patented use because the off-patented treatment of severe chronic pain more broadly included other categories: "[E]ven if severe chronic pain includes polyneuropathic pain, it also includes mononeuropathic pain and nociceptive pain." *Id.* In sum, *Grunenthal* was a case where encouraging treatment of patients with moderate to severe pain was not enough to induce the specific and patented treatment of polyneuropathic pain.

In contrast, this case involves a broader patented use that covers a larger patient population with HTG generally (triglycerides above 150 mg/dL) and an off-patent use that covers a narrower patient population with *severe* HTG (triglycerides above 500 mg/dL). Both *Grunenthal* and this case involve generic labels that pointed at a broader category of patients. The difference is that, in *Grunenthal*, that broader category of patients, i.e., those suffering from severe chronic pain, was tied to the off-patent indication. *Id*. Whereas here, the broader category of patients that Hikma's press releases and website identify, i.e., those with HTG generally, is associated with the patented use.

That distinction, misapplied by the district court, changes the factual question of what Hikma's conduct would have communicated to prescribing physicians. This

case is more like *GlaxoSmithKline*, where communications that the generic medication was therapeutically equivalent for a broad category of "heart failure" and as a general "cardiovascular agent" associated the generic with the broader patented use to treat congestive heart failure. 7 F.4th at 1335-36.

CONCLUSION

Amarin stated a claim for relief that was at least plausible. The order dismissing Amarin's first amended complaint should be reversed, and the case should be remanded for further proceedings.

Respectfully submitted,

PERKINS COIE LLP

by /s/Nathan K. Kelley

Nathan K. Kelley

Counsel for Appellants Amarin Pharma, Inc., Amarin Pharmaceuticals Ireland Ltd., and Mochida Pharmaceutical Co., Ltd.

ADDENDA

1. Memorandum Opinion, Order, and Final Judgment (Appx1-15)
2. Magistrate's Report and Recommendation (Appx1413-1430)
3. U.S. Patent No. 9,700,537 (Appx36-47)
4. U.S. Patent No. 10,568,861 (Appx77-129)

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMARIN PHARMA, INC., AMARIN PHARMACEUTICALS IRELAND LIMITED, MOCHIDA PHARMACEUTICAL CO., LTD. Plaintiffs; v. HIKMA PHARMACEUTICALS USA INC., HIKMA PHARMACEUTICALS PLC, AND HEALTH NET, LLC, Defendants.	Civil Action No. 20-1630-RGA-JLH

MEMORANDUM OPINION

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January 4, 2022

ANDREWS, U.S. DISTRICT JUDGE:

I referred this very interesting case to a magistrate judge. (D.I. 16). She wrote a Report and Recommendation on three pending motions to dismiss. (D.I. 64). Defendants filed objections (D.I. 70, 71), to which Plaintiffs responded (D.I. 77, 78). There is even an amicus brief. (D.I. 75). I heard oral argument on October 14, 2021. For the following reasons, I will ADOPT-IN-PART the Report and Recommendation. (D.I. 64). Hikma's motion to dismiss the First Amended Complaint (D.I. 19) is GRANTED. Hikma's motion to dismiss the original complaint (D.I. 11) is DISMISSED AS MOOT. Health Net's motion to dismiss the First Amended Complaint (D.I. 30) is DENIED.

I. BACKGROUND

Plaintiffs sued Defendants for induced infringement of three patents that describe methods of using icosapent ethyl for the reduction of cardiovascular risk. (D.I. 17). Plaintiffs manufacture and sell VASCEPA, a branded version of icosapent ethyl. (*Id.* at ¶¶ 1, 57-58). Defendant Hikma is a generic manufacturer of icosapent ethyl. (*Id.* at ¶ 1). Defendant Health Net is an insurer that provides coverage for Vascepa and Hikma's generic version. (*Id.* at ¶¶ 139-40).

II. LEGAL STANDARD

A motion to dismiss for failure to state a claim upon which relief may be granted is considered a dispositive motion. D. Del. LR 72.1(a)(3). A magistrate judge's Report and Recommendation regarding a case-dispositive motion is reviewed *de novo*. Fed. R. Civ. P. 72(b)(3).

When reviewing a motion to dismiss pursuant to Federal Rule of Civil Procedure 12(b)(6), the Court must accept the complaint's factual allegations as true. *See Bell Atl. Corp. v.*

Twombly, 550 U.S. 544, 555–56 (2007). Rule 8(a) requires "a short and plain statement of the claim showing that the pleader is entitled to relief." *Id.* at 555. The factual allegations do not have to be detailed, but they must provide more than labels, conclusions, or a "formulaic recitation" of the claim elements. *Id.* ("Factual allegations must be enough to raise a right to relief above the speculative level . . . on the assumption that all the allegations in the complaint are true (even if doubtful in fact)."). Moreover, there must be sufficient factual matter to state a facially plausible claim to relief. *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009). The facial plausibility standard is satisfied when the complaint's factual content "allows the court to draw the reasonable inference that the defendant is liable for the misconduct alleged." *Id.* ("Where a complaint pleads facts that are merely consistent with a defendant's liability, it stops short of the line between possibility and plausibility of entitlement to relief." (internal quotation marks omitted)).

Section 271(b) provides, "whoever actively induces infringement of a patent shall be liable as an infringer." 35. U.S.C. 271(b). To state a claim for induced infringement, the complaint must allege that there has been direct infringement, that the defendant knowingly induced infringement, and that the defendant has the intent to encourage another's infringement. *MEMC Elec. Materials, Inc. v. Mitsubishi Materials Silicon Corp.*, 420 F.3d 1369, 1378 (Fed. Cir. 2005). A generic manufacturer can be liable for inducing infringement of a patented method even when the generic has attempted to "carve out" the patented indications. *GlaxoSmithKline LLC v. Teva Pharmaceuticals USA*, Inc., 7 F.4th 1320, 1338 (Fed. Cir. 2021) (per curiam).

III. HIKMA'S MOTION TO DISMISS

A. BACKGROUND

Amarin sells Vascepa (icosapent ethyl) for the treatment of severe hypertriglyceridemia (the "SH indication") and cardiovascular risk reduction (the "CV indication"). (D.I. 17 at ¶¶ 1, 56). Only the CV indication is covered by Plaintiffs' patents. (*See* D.I. 22 at 1). Hikma received FDA approval to sell a generic version for the SH indication under the "skinny label" or "section viii carveout" regime. (D.I. 17 at ¶¶ 11, 95, 108). This regime allows a generic to sidestep the typical FDA requirement that a generic's labeling is the same as the brand's labeling. 21 U.S.C. §§ 355(j)(2)(A)(viii). The generic does so by removing the portions of the label associated with the patented use, resulting in a "skinny label." Plaintiffs allege that Defendant Hikma's label is "not-skinny-enough" and that the label, along with Hikma's public statements, induce infringement of Plaintiffs' patents for the CV indication. (D.I. 22 at 1).

B. DISCUSSION

1. The Federal Circuit's *GSK* Decision

Two days after the Report issued, the Court of Appeals issued the most recent authoritative opinion concerning skinny labels, albeit after the case was fully litigated in the district court. *See GlaxoSmithKline LLC v. Teva Pharmaceuticals USA, Inc.* [hereinafter "*GSK*"], 7 F.4th 1320 (Fed. Cir. 2021). The Federal Circuit affirmed a jury's findings that Teva's "partial label" induced infringement of GSK's patent, notwithstanding Teva's attempt to exclude the patented use from its label under the skinny label regime. (*Id.* at 1338). Ultimately, the Federal Circuit concluded, "Teva's partial label did not successfully carve out the patented use, and thus, Teva was selling its generic with a label which infringed the method claim." *Id.* Accordingly, Teva's label was "not a skinny label." *Id.* at 1328.

The Federal Circuit also found that two Teva press releases supported the jury's verdict. *Id.* at 1335-37. The first press release advertised Teva's drug as "indicated for treatment of heart failure" and did "not parse between congestive heart failure [the patented indication] or post-MI LVD [an unpatented indication]." *Id.* at 1336. The second press release stated that Teva received approval to market "its Generic version of GlaxoSmithKline's cardiovascular agent Coreg." *Id.* Expert testimony established that the phrase "'cardiovascular agent' 'indicated to doctors they could use Teva's carvedilol 'for all indications,' including heart failure." *Id.*

The Court held that *GSK* is a "narrow, case-specific review" and that it is still the law that "generics could *not* be held liable for merely marketing and selling under a 'skinny' label omitting all patented indications, or for merely noting (without mentioning any infringing uses) that FDA had rated a product as therapeutically equivalent to a brand-name drug." *Id.* at 1326. An "AB rating," as the complaint explains, "reflects a decision [by the FDA] that a generic drug is therapeutically equivalent to a branded drug when the generic drug is used as labeled[.]" (D.I. 17 at ¶ 98). As *GSK*'s discussion of Teva's press releases illustrates, where a generic label does not effectively carve out a patented use, advertisement that the drug is "AB rated" can support a finding of inducement. *GSK*, 7 F.4th at 1335.

2. Amarin's Complaint

Amarin's complaint pleads several factual allegations in support of its claim that Hikma induces infringement. These allegations fall into two categories: Hikma's label and Hikma's public statements. The Magistrate Judge recommends I deny Hikma's motion to dismiss because "several . . . portions of Hikma's label, taken together with Hikma's public statements, instruct physicians to use Hikma's product in a way that infringes the asserted patents." (D.I. 64 at 12).

The bulk of the briefing and oral argument was directed to Hikma's label, and I will address those arguments first.

As to the label, Hikma objects that Amarin's complaint fails to plead instruction as to at least two claim limitations—the requirement that icosapent ethyl be administered to reduce CV risk and the requirement to co-administer with a statin. (D.I. 71 at 7-8). Because I agree with Hikma that there has been no instruction as to CV risk reduction, I will not address Hikma's argument regarding co-administration with a statin.

Amarin contends that Hikma's label teaches CV risk reduction for two reasons. First, Hikma's label contains a notice regarding side effects for patients with CV disease. (D.I. 78 at 5-6). Second, Hikma's label does not "state that Hikma's 'generic version' of VASCEPA should not be used for the CV Indication or that the effect of icosapent ethyl on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined" (the "CV limitation"). (D.I. 17 at ¶¶ 108, 121). Hikma responds that (1) the notice regarding side effects is a warning and thus not an instruction to use icosapent ethyl to reduce cardiovascular risk, and (2) the removal of the CV risk reduction limitation is mere silence and that Hikma has no duty to discourage infringing use.

Regarding the warning as to side effects, I agree with Hikma. The label states, "Icosapent ethyl may cause serious side effects, including: … Heart rhythm problems which can be serious and cause hospitalization have happened in people who take icosapent ethyl, especially in people who have heart (cardiovascular) disease or diabetes with a risk factor for heart (cardiovascular) disease[.]" (D.I. 17, Ex. K at 12-13 of 15). This is hardly instruction or encouragement. *See, e.g.*, *Otsuka Pharm. Co. v. Torrent Pharms. Ltd.*, 99 F. Supp. 3d 461, 490 (D.N.J. 2015) ("[A] warning is just that—a warning. It is not an instruction[.]").

Amarin also argues that Hikma "removed"[1] the CV limitation from its label, which would be "understood in the field to teach that Hikma's product *has* been proven to reduce CV risk and to encourage its use for that purpose" because other drugs in the same class have not been shown to reduce CV risk. (D.I. 78 at 4). This amounts to an "affirmative statement" that it can be used for cardiovascular risk reduction, according to Plaintiffs. (D.I. 85 at 62:16-62:5).

The Federal Circuit has previously rejected the argument that generic labels must contain a "clear statement" discouraging use of the patented indication. *Takeda Pharms. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 632 n.4 (Fed. Cir. 2015). Plaintiffs must plead that "Hikma took affirmative steps to induce, not affirmative steps to make sure others avoid infringement." *Id.* Even if Plaintiffs are right that Hikma's label's silence regarding CV risk reduction communicates to the public that icosapent ethyl can be used to reduce CV risk, "merely describing an infringing mode is not the same as recommending, encouraging, or promoting an infringing use." *Id.* at 631 (cleaned up). I therefore find that the lack of a CV limitation on Hikma's label does not plausibly teach CV risk reduction.

Since I find that the label does not instruct CV risk reduction, the question is whether Hikma's public statements, including press releases and Hikma's website, induce infringement. (D.I. 17 at ¶ 127). Hikma's press releases state that its product is the "generic equivalent to Vascepa®" and that "Vascepa is a prescription medicine that is indicated, *in part*, as an adjunct to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL)

[1] Hikma contests Plaintiffs' use of the word "removal," noting, "*Amarin* removed the limitation of use from Vascepa's label *before* Hikma launched its product, and Hikma was required to use 'the same [labeling] as the labeling approved for the listed drug.'" (D.I. 71 at 7 n.2 (citing 21 U.S.C. § 355(j)(2)(A)(v))). The facts pled in the complaint state that the removal happened during the FDA approval process. (D.I. 17 at ¶ 108). At any rate, it appears that there is no allegation that Hikma's product was ever marketed with a label containing the CV limitation.

hypertriglyceridemia. According to IQVIA, US sales of Vascepa® were approximately $919 million in the 12 months ending February 2020." (*Id.* at ¶ 112). The sales figures cited by Hikma include Vascepa's sales of the patented indication. The complaint further alleges that Hikma's website states that Hikma's generic is "AB rated" in the "Therapeutic Category: Hypertriglyceridemia." (*Id.* at ¶ 125).

Hikma's press releases might be relevant to intent but they do not support actual inducement. Hikma's advertising of icosapent ethyl as the "generic equivalent" of Vascepa does not expose Hikma to liability. *GSK*, 7 F.4th at 1335 n.7. The citation of Vascepa's sales figures go to Hikma's intent to induce. Intent alone is not enough; Amarin must plead an inducing act.

Amarin also alleges that Hikma's website induces infringement by advertising its product in the therapeutic category "hypertriglyceridemia." The complaint pleads, "hypertriglyceridemia . . . does not match and is broader than the Indications and Usage sections of Hikma's Label, which includes only Severe Hypertriglyceridemia Indication (i.e., triglycerides ≥500 mg/dL)." (D.I. 17 at ¶ 126). Accepting the facts in the light most favorable to Amarin, Amarin has pled that the category "hypertriglyceridemia" includes infringing uses. The question is whether this is enough, without a label or other public statements instructing as to infringing use, to induce infringement.

I hold that it is not. This statement does not rise to the level of encouraging, recommending, or promoting taking Hikma's generic for the reduction of CV risk.

Two recent Federal Circuit cases are instructive on this point. The *GSK* majority found that Teva's advertising of "its Generic version of GlaxoSmithKline's cardiovascular agent," when "cardiovascular agent" was a category that included both infringing and non-infringing uses, supported a jury's finding of inducement. 7 F.4th at 1336. The Court emphasized that:

> Teva did not merely say its drug is a cardiovascular agent, leaving the world to wonder about its uses. It said its product is a generic equivalent of GSK's cardiovascular agent Coreg®. It was reasonable for the jury to conclude, especially in light of the prior press release that expressly mentioned heart failure, that Teva was again encouraging the substitution of its product for all of Coreg's® cardiovascular indications, including as claimed in the '000 patent.

Id. at 1337. In contrast, the Federal Circuit has found that a label indicated for "[m]oderate to severe chronic pain," which included both infringing and non-infringing uses, did "not specifically encourage use" of the generic for the patented treatment. *Grunenthal GMBH v. Alkem Lab'ys Ltd.*, 919 F.3d 1333, 1339 (Fed. Cir. 2019) ("[E]ven if severe chronic pain includes polyneuropathic pain, it also includes mononeuropathic pain and nociceptive pain. Therefore, the proposed ANDA labels do not specifically encourage use of tapentadol hydrochloride for treatment of polyneuropathic pain.").

Here, Hikma stated that its product was "AB Rated" in a category that includes both patented and non-patented uses. The "AB rating" points to the label, as the *GSK* court explained:

> We do not hold that an AB rating in a true section viii carve-out (one in which a label was produced that had no infringing indications) would be evidence of inducement. In this case, Teva's representation of AB rating would point physicians to its partial label, which, for the reasons above, the jury was free to credit as evidence of induced infringement.

GSK, 7 F.4th at 1335 n.7. Unlike Teva's press release in *GSK*, Hikma has not pointed to Vascepa's patented uses in describing itself as Vascepa's generic equivalent. This case is more like *Grunenthal*, where the broader category simply includes both infringing and non-infringing uses, without "specifically encourage[ing]" the use of the generic for the non-infringing uses. 919 F.3d at 1339.

Since I find that Amarin's complaint has failed to plead inducement based on Hikma's label or public statements, I will grant Hikma's motion to dismiss.

IV. HEALTH NET'S MOTION TO DISMISS

A. BACKGROUND

Defendant Health Net provides insurance coverage for Plaintiffs' branded Vascepa and Defendant Hikma's generic version. According to Plaintiffs, Health Net's formulary placement induces infringement of Plaintiffs' patents by encouraging the use of Hikma's generic for the CV indication. Health Net's formulary lists Hikma's generic in a lower tier than Amarin's Vascepa, resulting in lower copays when a patient opts for Hikma's generic. (D.I. 17 at ¶ 143). Since it is common for pharmacies to automatically substitute an AB-rated generic such as Hikma's for the branded version, Plaintiffs allege that this formulary placement leads to substitution on "all VESCEPA prescriptions, not just the prescriptions directed to the" SH indication. (*Id.* at ¶ 151).

B. DISCUSSION

The Report recommends I deny Health Net's motion to dismiss because there are factual questions regarding whether Health Net has taken an affirmative act to induce infringement and whether Health Net's actions actually cause others to infringe. (D.I. 64 at 17). Health Net objects, "Plaintiffs fail to allege facts (not conclusions or speculation) supporting a plausible conclusion that Health Net was aware of the asserted patents, and once aware, took affirmative steps with the specific intent to induce another's infringement of those patents—rather than merely acting despite knowledge that others may infringe." (D.I. 70 at 2). I disagree.

I find that the complaint pleads enough facts to plausibly allege knowledge of the asserted patents. Amarin sent a pre-suit letter to its point of contact for Health Net. (D.I. 17 at ¶ 87). It is true that the pre-suit letter did not specify the patent numbers. However, the letter states that Amarin has patent exclusivity for the CV indication, and the complaint elsewhere pleads that the patents associated with the CV indication are readily available through a resource

well-known in the industry, the FDA's Orange Book. (*Id.* at ¶¶ 84, 88). Thus, I agree with the Magistrate Judge that these facts, taken together in the light most favorable to the Plaintiffs, make it plausible that Health Net had specific knowledge of the patents at issue.

Read in the light most favorable to Amarin, the complaint also plausibly alleges affirmative acts taken with a specific intent to induce another's infringement. Formulary selection and the prior authorization process, as pled, could be affirmative acts under the law of induced infringement. Health Net argues that the selection of its formulary is automatic, based on Plaintiff's own pricing as compared to the generic. (D.I. 85 at 75:5-12 (noting that "this is done by a computer program")). This may be true, but it is not a shield. Health Net added generic icosapent ethyl capsules to its formularies. (D.I. 17 at ¶¶ 140-143). It is immaterial whether the placement was done by a human or a computer.

Amarin also plausibly pleads specific intent to induce. At the very least, Health Net's prior authorization form supports an inference of specific intent because it lists the patented indication on the generic icosapent ethyl capsules form. (D.I. 17 at ¶ 159). Health Net's placement of generic icosapent ethyl on a preferred tier encourages the substitution of the generic for the branded drug, including for the patented indication. (*Id.* at ¶¶ 145, 151). Together, this is enough to plead specific intent to induce.

In its objections, Health Net argues that the "preferred" language in its formularies cannot be an active step because they are required by state law to disclose which drugs are "preferred." (*Id.* at 5). This may be true, but it is not the language of the formulary that is at issue; it is the incentives the formulary puts in place. (*See id.* at ¶¶ 145, 151).

Health Net stresses that they are just a payer, not the physician writing the prescription nor the pharmacist making the substitution. (D.I. 70 at 9). As the Report points out, "It may …

turn out that, despite knowledge of infringement by its beneficiaries and their providers, Health Net's actions in selecting its formulary and adopting its prior authorization procedure … do not, in fact, influence the decisions of beneficiaries, pharmacists, and medical providers to use, dispense, and prescribe Hikma's generic product in an infringing way[.]" (D.I. 64 at 17; *see Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003) ("[I]f a physician, without inducement by Apotex, prescribes a use of gabapentin in an infringing manner, Apotex's knowledge is legally irrelevant. In the absence of any evidence that Apotex has or will promote or encourage doctors to infringe the neurodegenerative method patent, there has been raised no genuine issue of material fact.")). These are factual questions that cannot be resolved on a motion to dismiss.

Ultimately, I agree with the Magistrate Judge that Plaintiffs have pled enough to proceed with their case against Health Net.

V. CONCLUSION

An appropriate order will follow.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMARIN PHARMA, INC., AMARIN PHARMACEUTICALS IRELAND LIMITED, MOCHIDA PHARMACEUTICAL CO., LTD. Plaintiffs; v. HIKMA PHARMACEUTICALS USA INC., HIKMA PHARMACEUTICALS PLC, AND HEALTH NET, LLC, Defendants.	Civil Action No. 20-1630-RGA-JLH

ORDER

For the reasons stated in the accompanying Memorandum Opinion, Hikma's motion to dismiss the First Amended Complaint (D.I. 19) is **GRANTED**. Hikma's motion to dismiss the original complaint (D.I. 11) is **DISMISSED AS MOOT**. Health Net's motion to dismiss the First Amended Complaint (D.I. 30) is **DENIED**. The first amended complaint (D.I. 17) as to the Hikma Defendants is **DISMISSED** without prejudice.[1]

IT IS SO ORDERED this 4th day of January 2022.

United States District Judge

[1] Plaintiffs requested leave to amend if the first amended complaint was dismissed. (D.I. 22 at 20). Plaintiffs gave no indication as to what more they could plead, but if they have something more, they may file a motion in compliance with the Local Rules seeking leave to amend.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTICT OF DELAWARE

AMARIN PHARMA, INC., AMARIN PHARMACEUTICALS IRELAND LIMITED, MOCHIDA PHARMACEUTICAL CO., LTD.,	:	
Plaintiffs,	:	
v.	:	C.A. No. 20-1630-RGA-JLH
HIKMA PHARMACEUTICALS USA INC., HIKMA PHARMACEUTICALS PLC, AND HEALTH NET, LLC	:	
Defendants.	:	

FINAL JUDGMENT UNDER
FEDERAL RULE OF CIVIL PROCEDURE 54(b)

THIS MATTER having come before the Court on Defendants Hikma Pharmaceuticals USA Inc. and Hikma Pharmaceuticals PLC's (collectively, "Hikma") Motion for Entry of Final and Appealable Judgment under Federal Rule of Civil Procedure 54(b), and the Court having considered Hikma's arguments and submissions in support of the Motion;

It is hereby **ORDERED** that the Motion is **GRANTED**.

For the reasons set forth by Hikma in its moving papers, the Court finds that the Court's order granting Hikma's motion to dismiss Plaintiffs' first amended complaint (D.I. 98) is a final judgment resolving Plaintiffs' claims against Hikma, and the Court expressly determines that there is no just reason for delay (*see* Fed. R. Civ. P. 54(b)).

Considering the factors set forth in *Berckeley Inv. Grp., Ltd. v. Colkitt*, 455 F.3d 195, 203 (3d Cir. 2006), the Court finds that (1) the relationship between the adjudicated claims against Hikma and the unadjudicated claims against the remaining Defendant, Health Net, LLC, is

minimal because Plaintiff's theories of infringement against these respective defendants are materially different; (2) the only foreseeable possibility that the need for review might be mooted by future developments in this Court is the invalidation of the asserted patents, which is unlikely to occur for more than a year; (3) the possibility that the reviewing court might be obliged to consider the same issue a second time is minimal because any appeal of the Court's order granting Hikma's motion to dismiss does not relate to Plaintiffs' infringement theory against Health Net; (4) there is no claim or counterclaim which could result in a set-off against the judgment sought to be made final; and (5) no miscellaneous factors (such as delay, economic and solvency considerations, shortening the time of trial, frivolity of competing claims, expense, and the like) weigh against entering final judgment at this time.

Accordingly, final judgment is **ENTERED** in favor of Hikma and against Plaintiffs; Plaintiffs' claims against Hikma in this action are **DISMISSED WITH PREJUDICE**; and each party shall bear its own costs and fees.

IT IS SO ORDERED this 13th day of October, 2022.

Honorable Richard G. Andrews
United States District Court Judge

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMARIN PHARMA, INC., AMARIN PHARMACEUTICALS IRELAND LIMITED, MOCHIDA PHARMACEUTICAL CO., LTD.,	)	
Plaintiffs,	)	
v.	)	C.A. No. 20-1630-RGA-JLH
HIKMA PHARMACEUTICALS USA INC., HIKMA PHARMACEUTICALS PLC, AND HEALTH NET, LLC,	)	
Defendants.	)	

REPORT AND RECOMMENDATION

Plaintiffs Amarin Pharma, Inc., Amarin Pharmaceuticals Ireland Limited (collectively, "Amarin"), and Mochida Pharmaceutical Co., Ltd. ("Mochida") filed this suit against Defendants Hikma Pharmaceuticals USA Inc., Hikma Pharmaceuticals PLC (collectively, "Hikma"), and Health Net, LLC ("Health Net"). Plaintiffs allege that Hikma and Health Net have each induced infringement of U.S. Patent Nos. 9,700,537 (the '537 patent), 8,642,077 (the '077 patent), and 10,568,861 (the '861 patent) under 35 U.S.C. § 271(b). Hikma and Health Net have separately moved to dismiss under Federal Rule of Civil Procedure 12(b)(6).

Plaintiffs' infringement case against Hikma is what is referred to by those in the know as a "skinny label" case. Amarin developed and markets a branded prescription drug that has two FDA-approved indications. One of those indications is patented, the other is not. Hikma launched a generic version after receiving FDA approval for the non-patented indication only. Notwithstanding the limited approval, Plaintiffs allege that Hikma—through its product label,

website, and press releases—instructs and encourages physicians to use its generic version for the patented indication, making Hikma liable for inducing infringement under 35 U.S.C. § 271(b).

Plaintiffs have an entirely different (and apparently novel) theory as to Health Net. Health Net is a health insurance provider. It does not prescribe drugs, but it does pay for drugs that are prescribed to its beneficiaries by physicians. Plaintiffs allege that the way that Health Net has set up its approval and payment process for Amarin's product and Hikma's generic version amounts to active encouragement to use Hikma's generic version for the patented indication, making Health Net liable for inducing infringement under 35 U.S.C. § 271(b).

This case is at the pleadings stage. I cannot make factual findings about what Hikma's label and advertisements communicate to physicians. Nor is it appropriate at this stage to make findings about how Health Net's prescription drug coverage operates and whether it actually has any effect on anyone's decision to use Hikma's product for the patented use. The only determination at this stage is whether Plaintiffs' allegations state plausible claims for relief.

"The plausibility standard is not akin to a 'probability requirement,'"[1] and "a well-pleaded complaint may proceed even if it strikes a savvy judge that actual proof of the facts alleged is improbable, and that a recovery is very remote and unlikely."[2] I conclude that Plaintiffs' claims satisfy the plausibility standard. According, I recommend that both motions to dismiss be DENIED.

[1] *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009) (quoting *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 556 (2007)).

[2] *Twombly*, 550 U.S. at 556 (2007) (internal marks omitted).

I. BACKGROUND

The statutory scheme for obtaining FDA approval of a generic drug for only non-patented uses has been well explained in numerous cases and I could do no better here.[3] Accordingly, this Report and Recommendation assumes familiarity with the key features of the Hatch-Waxman generic drug approval process as it relates to "carve out" labels (aka "skinny" labels) and associated infringement litigation.

A. Amarin's VASCEPA®[4]

The active ingredient in Amarin's Vascepa product is icosapent ethyl, an ethyl ester of an omega-3 fatty acid (EPA) commonly found in fish oils. (D.I. 17 ¶¶ 25, 28, 54, Ex. D.) Vascepa currently has two FDA-approved indications: (1) treatment of severe hypertriglyceridemia (the "SH indication"); and (2) cardiovascular risk reduction (the "CV indication"). (*Id.* ¶¶ 1, 56.)

Severe hypertriglyceridemia (SH) is a condition where patients have triglyceride levels greater than 500 mg/dL. (*Id.* ¶ 30, Ex. D.) Vascepa received FDA approval for the SH indication in 2012. (*Id.* ¶ 30.) At that time, and up until 2019, the Vascepa label contained the following "limitation of use" regarding the CV indication: "The effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined." (*Id.* ¶ 60, Exs. E, F.)

After receiving FDA approval to market Vascepa for the SH indication, Amarin conducted further clinical studies to examine the effects of Vascepa on cardiovascular risk reduction. (*Id.*

[3] *See, e.g., AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1045-46 (Fed. Cir. 2010) (describing Hatch-Waxman scheme and carve out labels); *GlaxoSmithKline LLC v. Teva Pharms. USA, Inc.*, No. 14-878-LPS-CJB, 2016 WL 3946770, at *2-3 (D. Del. July 20, 2016) (same), *report and recommendation adopted*, No. 14-878-LPS-CJB, 2017 WL 1050574 (D. Del. Mar. 20, 2017).

[4] I assume the facts alleged in Plaintiffs' First Amended Complaint to be true for purposes of resolving the motions to dismiss for failure to state a claim. *Iqbal*, 556 U.S. at 678.

¶¶ 31-33.) One clinical study assessed the effectiveness of Vascepa as an add-on to statin therapy to reduce major cardiovascular events in patients with persistent elevated triglycerides. (*Id.* ¶ 33.) Based on the results of the study, the FDA approved Vascepa in December 2019 for the CV indication, that is, "as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥ 150 mg/dL) and established cardiovascular disease or diabetes mellitus and 2 or more additional risk factors for cardiovascular disease." (*Id.* ¶ 34, Ex. D.) When the FDA approved the use of Vascepa for the CV indication, Amarin was permitted to add the CV indication to the Vascepa label and remove the CV limitation of use. (*Id.* ¶ 63; *compare id.*, Ex. D *with id.*, Exs. E, F.)

B. The asserted patents

Plaintiffs have patents covering methods of using icosapent ethyl to reduce the risk of cardiovascular events in patients. The '537 patent was issued on July 11, 2017 and is assigned to Mochida. Amarin has an exclusive license. (*Id.* ¶¶ 41-43.) Claim 1 of the '537 patent describes a method of reducing the risk of a cardiovascular event by administering icosapent ethyl with a statin to a patient with high cholesterol, elevated triglycerides, and reduced HDL-C (good cholesterol).[5] It recites as follows:

> 1. A method of reducing occurrence of a cardiovascular event in a hypercholesterolemia patient consisting of:
>
> identifying a patient having triglycerides (TG) of at least 150 mg/DL and HDL-C of less than 40 mg/dL in a blood sample taken from the patient as a risk factor of a cardiovascular event, wherein the patient has not previously had a cardiovascular event, and administering ethyl icosapentate in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor,
>
> wherein said 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitor is administered to the patient at least one of before, during and after

[5] I am attempting to describe the invention in a way that facilitates ease of understanding. In so doing, I make some generalizations about the claim elements. Nothing I say here should be taken as the Court's views on any current or future claim construction (or any other) issues.

administering the ethyl icosapentate; and

wherein the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor is selected from the group consisting of pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin, pitavastatin, rosuvastatin, and salts thereof, and

wherein daily dose of the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor are 5 to 60 mg for pravastatin, 2.5 to 60 mg for simvastatin, 10 to 180 mg for fluvastatin sodium, 5 to 120 mg for atorvastatin calcium hydrate, 0.5 to 12 mg for pitavastatin calcium, 1.25 to 60 mg for rosuvastatin calcium, 5 to 160 mg for lovastatin, and 0.075 to 0.9 mg for cerivastatin sodium.

(*Id.*, Ex. C ('537 Patent).)

The '077 patent was issued on February 4, 2014 and is assigned to Amarin. (*Id.* ¶¶ 46-48.) Claim 1 describes a method of reducing triglycerides in a patient with mixed dyslipidemia (abnormal lipid levels) on statin therapy by administering icosapent ethyl. Claims 1 and 8 of the '077 patent recite as follows:

1. A method of reducing triglycerides in a subject with mixed dyslipidemia on statin therapy comprising, administering to the subject a pharmaceutical composition comprising about 2500 mg to 5000 mg per day of ethyl eicosapentaenoate and not more than about 5%, by weight of all fatty acids, docosahexaenoic acid or its esters to effect a reduction in fasting triglyceride levels in the subject.

8. The method of claim 1 wherein the subject exhibits a reduction in hs-CRP compared to placebo control.

(*Id.*, Ex. O ('077 Patent).)

The '861 patent was issued on February 25, 2020. It is also assigned to Amarin. (*Id.* ¶¶ 50-52.) Claim 1 describes a method of reducing the risk of cardiovascular death in a patient with established cardiovascular disease by administering icosapent ethyl. Dependent claim 2 specifies that the patient must have a triglyceride level "of about 135 mg/dL to about 500 mg/dL" (*i.e.*, potentially elevated but not necessarily severely high) and an LDL-C (bad cholesterol) level within a specified range. Claims 1 and 2 of the '861 patent recite as follows:

1. A method of reducing risk of cardiovascular death in a subject with established cardiovascular disease, the method comprising administering to said subject about 4 g of

ethyl icosapentate per day for a period effective to reduce risk of cardiovascular death in the subject.

2. The method of claim 1, wherein the subject has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL and a fasting baseline LDL-C level of about 40 mg/dL to about 100 mg/dL.

(*Id.*, Ex. P ('861 Patent).)

After Amarin received FDA approval for the CV indication, it listed the '537, '077, and '861 patents (the "asserted patents") in the Orange Book for Vascepa. (*Id.* ¶¶ 70-79.)

C. Hikma's generic product

On November 5, 2020, Hikma launched a generic version of Vascepa after receiving FDA approval of its Abbreviated New Drug Application (ANDA). (*Id.* ¶¶ 11, 13.) Hikma's ANDA contained a so-called "section viii carve out" regarding the asserted patents. (*Id.* ¶¶ 104, 105.) That is, Hikma represented to the FDA that it would not market its generic product for the uses covered by those patents.

When Hikma originally submitted its ANDA in 2016, it only sought approval for the SH indication, as the FDA had not yet approved Vascepa for the CV indication. (*Id.* ¶ 108.) At that time, Hikma's proposed generic label (like the Vascepa label at that time) referred only to the SH indication and contained the CV limitation of use. (*Id.*) After Amarin received approval for the CV indication and listed the asserted patents in the Orange Book, Hikma submitted section viii statements with respect to those patents. (*Id.* ¶¶ 104, 108.) Hikma did not propose to add the CV indication to its label, but Hikma did remove the CV limitation of use from its proposed label. (*Id.* ¶ 108.)

The FDA approved Hikma's ANDA on May 21, 2020. (*Id.* ¶ 105.) The "Indications and Usage" section of Hikma's approved label refers only to the SH indication, but it does not contain the CV limitation of use. (*Id.*, ¶ 107 Ex. K.) By the time Hikma's product hit the market in

November 2020, the majority of doctors who prescribed Vascepa did so for uses other than the SH indication, and Hikma was aware of that fact. (*Id.* ¶ 110.)

Hikma issued press releases in 2020 regarding its generic product. In a March 31, 2020 press release, Hikma referred to its then-unapproved product as a "generic version of Amarin Corporation's Vascepa® 1 gm (icosapent ethyl) capsules." (*Id.* ¶¶ 111-113, Ex. L.) The press release further stated that "Vascepa® is a prescription medicine that is indicated, *in part*, as an adjunct to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia" (emphasis added), and that the prior year's "US sales of Vascepa® were approximately $919 million." (*Id.*) The Vascepa sales figure cited by Hikma in the press release included sales for the CV indication, and Hikma knew that. (*Id.*) Hikma issued another press release on September 3, 2020 that contained similar statements. (*Id.* ¶¶ 118-120, Ex. M.) Hikma's March and September 2020 press releases were still accessible on Hikma's website when Plaintiffs filed this action. (*Id.* ¶¶ 117, 124.)

Hikma's website also advertises its generic version as being "AB" rated in the "Therapeutic Category: Hypertriglyceridemia." (*Id.* ¶ 125-126, Ex. T.) That webpage does not refer to the fact that Hikma's product is only FDA-approved for "severe hypertriglyceridemia." (*Id.*)

According to the First Amended Complaint, Hikma's label, press releases, and website "instruct, promote, and encourage" healthcare providers and patients to administer Hikma's product in a way that infringes the asserted patents. (*Id.* ¶ 127.)

D. Health Net

Health Net is a health insurance provider. (*Id.* ¶ 137.) Vascepa is covered by Health Net's insurance plans and appears on Health Net's formularies as a covered drug. (*Id.* ¶ 139.) When Hikma launched its generic version, Health Net added the generic to its formularies, meaning that

it would provide insurance coverage and/or payment for Hikma's product. (*Id.* ¶ 140.) Some of Health Net's formularies currently list Hikma's generic version as a Tier 1 drug and Vascepa as a Tier 3 drug. (*Id.* ¶¶ 143, 157.) The result is that plan beneficiaries have to pay a higher copay for Vascepa than they do for Hikma's generic version. (*Id.* ¶ 145.)

At least one of Health Net's plans requires "Prior Authorization" before it will cover and pay for either Vascepa or Hikma's generic version. (*Id.* ¶¶ 153, 159.) To obtain prior authorization from the plan, the patient's medical provider must submit documentation demonstrating that the prescription is being given for either the SH or the CV indication.[6] (*Id.* ¶¶ 153, 154, 159, 160, Exs. EE, HH.)

Plaintiffs allege that Health Net is aware that use of Hikma's generic for the CV indication infringes Plaintiffs' patents because (among other reasons) Plaintiffs sent a letter in December 2020 to Mr. Mike Flynn at Envolve Pharmacy Solutions, Inc. (*Id.* ¶ 87.) Envolve is Health Net's Pharmacy Benefit Manager, and Mr. Flynn is Amarin's point of contact for both Envolve and Health Net. (*Id.*) The letter stated that "[t]he Hikma generic does not have an FDA-approved indication for CV risk reduction." (*Id.* ¶¶ 87-90, Ex. GG.) The letter further stated that Amarin "had sued Hikma for patent infringement for encouraging use of its generic product in the CV risk reduction indication" and that "the Hikma generic should not be dispensed for this indication." (*Id.*)

[6] For example, Health Net's Essential Drug List formulary requires a prior authorization before covering either Vascepa or Hikma's generic version. The prior authorization has criteria that (Amarin contends) map to the SH indication and the CV indication:

> (1) "Hypertriglyceridemia without ASCVD," where the patient has "[f]asting triglycerides ≥ 500 mg/dL," or
> (2) "Reduction of Cardiovascular Disease Risk" with "[d]ocumentation (labs must be within 90 days) of fasting triglycerides between 150-499 mg/dL" and, "[f]or members on statin therapy," "Vascepa is prescribed in conjunction with a statin at the maximally tolerated dose."

(*Id.* ¶ 153, Ex. HH; *see also id.* ¶¶ 154, 159-60, Ex. EE.)

According to the First Amended Complaint, Health Net's implementation of the above-described formulary and prior authorization arrangement amounts to encouragement to providers and patients to administer Hikma's product for the CV indication, which, Plaintiffs allege, results in infringement of the asserted patents.

E. Procedural background

Plaintiffs filed their original Complaint on November 30, 2020. (D.I. 1.) The original Complaint only contained claims against Hikma. On January 4, 2021, Hikma filed a motion to dismiss the Complaint for failure to state a claim. (D.I. 11.)

On January 25, 2021, Plaintiffs filed a First Amended Complaint. (D.I. 17.) The First Amended Complaint added new factual allegations against Hikma and added new claims against Health Net. Counts I-III allege that Hikma induces infringement of the '537, '077, and '861 patents under 35 U.S.C. § 271(b). Counts IV-VI allege that Health Net induces infringement of the '537, '077, and '861 patents under 35 U.S.C. § 271(b).

Hikma and Health Net each filed motions to dismiss the claims against them for failure to state a claim. (D.I. 19; D.I. 30.) Health Net also moved to sever Plaintiffs' claims against Health Net from Plaintiffs' claims against Hikma. (D.I. 32.) The Court heard oral argument on all pending motions on May 26, 2021. This is my Report and Recommendation on Hikma's and Health Net's motions to dismiss.

II. LEGAL STANDARD

A defendant may move to dismiss a complaint under Federal Rule of Civil Procedure 12(b)(6) for failure to state a claim. "To survive a motion to dismiss, a complaint must contain sufficient factual matter, accepted as true, to 'state a claim to relief that is plausible on its face.'" *Iqbal*, 556 U.S at 678 (quoting *Twombly*, 550 U.S. at 570). A claim is plausible on its face when the complaint contains "factual content that allows the court to draw the reasonable inference that the defendant is liable for the misconduct alleged." *Id.* (citing *Twombly*, 550 U.S. at 556). A possibility of relief is not enough. *Id.* "Where a complaint pleads facts that are 'merely consistent with' a defendant's liability, it 'stops short of the line between possibility and plausibility of entitlement to relief.'" *Id.* (quoting *Twombly*, 550 U.S. at 557). In determining the sufficiency of the complaint under the plausibility standard, all "well-pleaded facts" are assumed to be true, but legal conclusions are not. *Id.* at 679.

III. DISCUSSION

Section 271(b) of Title 35 provides that "[w]hoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). To state a claim of induced infringement under § 271(b), the complaint must plausibly allege that (1) there has been direct infringement, (2) the defendant knowingly induced infringement, and (3) the defendant possessed the intent to encourage another's infringement. *MEMC Elec. Materials, Inc. v. Mitsubishi Materials Silicon Corp.*, 420 F.3d 1369, 1378 (Fed. Cir. 2005); *FO2GO LLC v. KeepItSafe, Inc.*, No. 18-807-RGA, 2019 WL 1615398, at *3 (D. Del. Apr. 16, 2019).

In the pharmaceutical drug context, a generic manufacturer can be liable under § 271(b) for inducing infringement of a patented method even where the FDA has not approved the generic

product for use in accordance with the patented method.[7] *See AstraZeneca*, 633 F.3d at 1056-61 (affirming district court's grant of preliminary injunction against generic manufacturer for inducing infringement of patented method under § 271(b) even though generic product was not approved for patented once-daily use); *GlaxoSmithKline*, 2016 WL 3946770, at *15 ("The decision in *AstraZeneca 2010* indicates that there can, in fact, be situations where a generic manufacturer seeks and obtains a section viii carve-out for a use of a drug that is (according to the FDA) a 'different' use from a patented use—and yet the generic's label could nevertheless be written in such a way that it evidences active steps to induce patent infringement."); *see also id.*, 2017 WL 1050574, at *1-2 (denying generic defendant's motion to dismiss inducement claim notwithstanding section viii carve out, where plaintiff alleged that defendant's label and other conduct encouraged use of the generic product in an infringing manner).

The assessment of whether a complaint plausibly alleges inducement in a pharmaceutical case is thus no different than the analysis in any other case. The court must determine whether the complaint plausibly alleges that the generic manufacturer "offer[ed] a product with the object of promoting its use to infringe, as shown by clear expression or other affirmative steps taken to foster infringement." *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1305-06 (Fed. Cir. 2006) (en banc in relevant part). Such "affirmative steps" may include allegations that a defendant "advertis[ed] an infringing use or instruct[ed] how to engage in an infringing use." *Takeda Pharms. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 630-31 (Fed. Cir. 2015) (quoting *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 935-36 (2005)).

To be clear, it is not enough to allege that a defendant had "mere knowledge" that its

[7] In contrast, in an ANDA case, a generic manufacturer cannot be liable under 35 U.S.C. § 271(e)(2) for infringing a method patent unless its ANDA seeks FDA approval for the patented use. *Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1321-22 (Fed. Cir. 2012); *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003).

product could be—or is being—used to infringe. *Warner-Lambert*, 316 F.3d at 1364. Rather, the allegations must plausibly suggest "culpable conduct, directed to encouraging another's infringement." *DSU Med.*, 471 F.3d at 1306. Moreover, a defendant who sells a product having substantial noninfringing uses has no duty to take affirmative steps to make sure that others avoid infringement. *Takeda*, 785 F.3d at 632 n.4.

A. Hikma

The First Amended Complaint alleges that Hikma's product label, press releases, and website encourage infringement of the asserted patents. Hikma contends that the claims against it must be dismissed because the allegations fail to state a plausible claim of inducement. I disagree.

The First Amended Complaint alleges that, notwithstanding the lack of an express instruction regarding the CV indication in the "Indications and Usage" section of Hikma's label, several other portions of Hikma's label, taken together with Hikma's public statements, instruct physicians to use Hikma's product in a way that infringes the asserted patents. For example, claim 1 of the '537 patent covers a method of treating hypercholesterolemia patients with elevated triglyceride (TG) levels of at least 150 mg/dL and HDL-C less than 40 mg/mL, and who are on a statin, in order to reduce the risk of a cardiovascular event. The "Dosage and Administration" section of Hikma's label instructs providers to "[a]ssess lipid levels before initiating therapy." (D.I. 17 ¶ 130, Ex. K § 2.1.) The "Indications and Usage" section instructs administration to patients with TG levels ≥ 500 mg/dL, which, by definition, is at least 150 mg/dL. In addition, the "Clinical Studies" section of Hikma's label describes treatment of patients with (1) median total cholesterol of 254 mg/dL (*i.e.*, hypercholesterolemia); (2) baseline TG levels between 500 and 2,000 mg/dL, with a median baseline of 684 mg/dL (*i.e.*, ≥ 150 mg/dL); (3) a median baseline HDL-C level of 27 mg/dL; and (4) with 25% of the patients on concomitant statin therapy. (*Id.*

¶ 130, Ex. K § 14.2.) The "Patient Information" section describes that the product may be used by patients at risk of having a cardiovascular event. (*Id.* Ex. K.) And, Hikma removed the CV limitation of use from its proposed label, which, according to Plaintiffs, "communicat[es] to the market that Hikma's generic product has been shown to reduce CV risk." (*Id.* ¶ 133.) The First Amended Complaint contains similar allegations regarding the '861 and '077 patents. (*Id.* ¶¶ 131, 134, Ex. K.)

The FAC further alleges that Hikma is aware that the majority of Vascepa prescriptions are for uses other than the SH indication and that Hikma's public statements encourage the use of its product for the same indications that Vascepa is used for. (*Id.* ¶¶ 110, 115, 122.) Plaintiffs point to Hikma's March and September 2020 press releases, which describe its product as a generic version of Vascepa and refer to sales figures that—Hikma knew—include sales for the CV indication. (*Id.* ¶¶ 111, 113, 118, 120.) Plaintiffs also point to Hikma's website, which advertises its generic version as "AB" rated in the "Therapeutic Category: Hypertriglyceridemia," which is broader than the "severe hypotriglyceridemia" (SH) indication for which it has FDA approval, and which may suggest administration to patients having merely elevated triglycerides as required by certain claims of the asserted patents. (*Id.* ¶¶ 125-126, Ex. T.)

Those allegations, taken together and viewed in the light most favorable to Plaintiffs, plausibly suggest the following: (1) that Hikma's label and public statements could instruct and/or encourage third parties to use its product for the CV indication, which Plaintiffs allege is covered by the asserted patents; and (2) that Hikma both knew and intended that third parties would use its product for that purpose. In my view, that is enough.

I am not persuaded by Hikma's arguments to the contrary. Hikma contends that Plaintiffs have not alleged sufficient "active steps" to encourage infringement. (D.I. 20 at 13-14.) But

Hikma's decision to continue to seek FDA approval after removing the CV limitation of use from its proposed label, its decision to sell its product accompanied by the current version of its label, and its public statements all constitute actions that are alleged to encourage infringement. And, at this stage, those allegations must be viewed in the light most favorable to Plaintiffs.

Hikma also points out that mere knowledge of direct infringement is insufficient to support an inducement claim. That is true. But Plaintiffs allege more than mere knowledge.

Hikma further points out that it has no duty to discourage infringement. Also true. But it cannot present information in a way that encourages infringement. The above-described allegations make it plausible that Hikma, rather than merely failing to prevent infringement, intended to cause others to infringe and knew that their acts would infringe.[8]

To the extent Hikma is suggesting that it cannot be liable for inducement absent FDA approval to use its product for CV therapy and/or explicit instructions in the "Indications and Usage" section of its label to use its product for a CV indication, I disagree. As explained above, lack of FDA approval for an infringing use does not preclude a finding of inducement. *See AstraZeneca*, 633 F.3d at 1060; *see also GlaxoSmithKline*, 2016 WL 3946770, at *13. Many of the cases relied on by Hikma at best establish that were this an ANDA case, and were Plaintiffs' allegations based solely on the label, Plaintiffs' inducement theory might lack merit as a matter of law.[9] But this is not an ANDA case, and Plaintiffs' allegations are not based solely on the label.

[8] Of course, in the absence of other evidence of intent, the Court could not find that Defendants are liable for inducement based solely on their failure to take affirmative steps to prevent others' infringement. But Defendants' knowledge that others are using Hikma's product in an infringing way, combined with their failure to take steps to deter such use, could be relevant to their intent to encourage others' infringement. *Cf. Grokster, Ltd.*, 545 U.S. at 939 n.12.

[9] *See, e.g., Bayer Schering*, 676 F.3d at 1321-24; *AstraZeneca LP v. Apotex, Inc.*, 669 F.3d 1370, 1378-1380 (Fed. Cir. 2012); *Warner-Lambert*, 316 F.3d at 1362-65; *see also GlaxoSmithKline*, 2017 WL 1050574, at *2 (acknowledging difference between claims under § 271(e)(2) and § 271(b)).

Hikma urges the Court to resolve this case at the pleadings stage, pointing out that the contents of its label and public statements are undisputed. But there is a real dispute about what those contents communicate to others, and I do not think it is appropriate to resolve it on a motion to dismiss. Stated another way, at this stage of the case, I am not prepared to say that Hikma's label and public statements—as a matter of law—could never amount to instruction and encouragement to infringe the asserted patents.

In support of its contention that its actions cannot constitute inducement, Hikma cites the Federal Circuit's opinions in *HZNP Medicines LLC v. Actavis Laboratories UT, Inc.*, 940 F.3d 680 (Fed. Cir. 2019), *Grunenthal GMBH v. Alkem Laboratories Ltd.*, 919 F.3d 1333 (Fed. Cir. 2019), and *Takeda*, 785 F.3d 625. But none of those cases was resolved at the motion to dismiss stage. *See HZNP*, 940 F.3d at 687-88 (bench trial); *Grunenthal*, 919 F.3d at 1338 (same); *Takeda*, 785 F.3d at 628 (preliminary injunction). And, unlike the allegations in this case, the evidence in those cases related solely to the effects of the generic labels. *See HZNP*, 940 F.3d at 702; *Grunenthal*, 919 F.3d at 1338-39 ("Here, [the plaintiffs] point only to the indications of the proposed labels as grounds for inducement . . . ."); *Takeda*, 785 F.3d at 632.[10]

I conclude that Plaintiffs have pleaded an inducement claim against Hikma that is at least plausible. While Hikma may be right that Plaintiffs will ultimately be unable to prove inducement, I cannot make that determination at this stage. I recommend that Hikma's motion to dismiss be denied.

B. Health Net

According to the First Amended Complaint, Health Net's implementation of its prior

[10] Moreover, while I need not decide whether Plaintiffs' allegations regarding the label alone state a plausible claim of inducement, I do note that the Federal Circuit in *Takeda* expressly declined to decide "whether evidence as to the invariable response of physicians could ever transform a vague label into active encouragement." *Takeda*, 785 F.3d at 632.

authorization process for icosapent ethyl prescriptions, combined with its placement of Hikma's generic on the formulary as a tier 1 drug and Vascepa as a tier 3 drug, amounts to encouragement to providers and patients to administer Hikma's product for the unapproved CV indication, which, Plaintiffs allege, results in infringement of the asserted patents.

To my knowledge, this is a novel theory. Neither side has cited any case in which a health insurer has been found liable to a pharmaceutical company for inducing infringement of a drug method of use patent. Viewing the allegations in the light most favorable to Plaintiffs, and in the absence of precedent to the contrary, I cannot say at this stage that Plaintiffs' theory is so implausible as to require dismissal at the pleadings stage.

The thrust of the allegations against Health Net are (1) that it provides coverage and payment for Hikma's generic product even in cases where Health Net actually knows that a particular beneficiary is using the generic version for an unapproved—and allegedly infringing—CV use, and (2) that Health Net actually encourages use of Hikma's product instead of Vascepa for the CV use because Health Net requires its beneficiaries to pay a higher copay for Vascepa than for Hikma's generic version, even when Hikma's version has been prescribed for the infringing/CV use. Plaintiffs allege that Health Net knows when a particular beneficiary is using Hikma's product for the CV use because Health Net's prior authorization process requires the beneficiary's provider to submit documentation supporting the use for which it has been prescribed. Plaintiffs further allege that Health Net had knowledge that its beneficiaries' use of Hikma's product for the CV indication amounted to infringement of Plaintiffs' patents because Amarin sent a pre-suit letter to its point of contact for Health Net informing it of that fact.[11] Taken

[11] While the letter did not identify the asserted patents by number, the First Amended Complaint plausibly alleges that "[i]t is known in the field, and Health Net would have been aware, that any patents covering a branded drug, such as VASCEPA®, are listed in the Orange Book." (D.I. 17 ¶ 84.)

together, and in the light most favorable to Plaintiffs, it is at least plausible that Health Net knowingly induced infringement and that it had specific intent to do so.

I understand Health Net's position that it merely provides coverage for drugs after they have been prescribed: it neither prescribes medication nor fills the prescriptions. It may ultimately turn out, as Health Net contends, that it has not taken any affirmative acts with the intent to foster infringement. It may also turn out that, despite knowledge of infringement by its beneficiaries and their providers, Health Net's actions in selecting its formulary and adopting its prior authorization procedure for icosapent ethyl prescriptions do not, in fact, influence the decisions of beneficiaries, pharmacists, and medical providers to use, dispense, and prescribe Hikma's generic product in an infringing way or otherwise encourage infringement. It may turn out, as Health Net contends, that "it is Plaintiffs' own pricing decision that encourages use of the generic product over Plaintiffs' brand product." (D.I. 31 at 17.) But all of those are factual issues that are inappropriate for resolution on a motion to dismiss. Plaintiffs allege otherwise, and Plaintiffs' allegations must be taken as true at this stage.

Like Hikma, Health Net points out that it has no duty to discourage others' infringement. While that is true, Plaintiffs also allege that Health Net took active steps—including adopting its formulary and prior authorization procedure for icosapent ethyl prescriptions and taking coverage and payment actions—that are alleged to encourage others' infringement.[12]

I again stress that I am not concluding that this novel claim against a health insurer will or is likely to succeed on the merits. I merely conclude that Plaintiffs have stated a plausible claim and can move forward with discovery.

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[12] *See also* n.8, *supra*.

IV. CONCLUSION

I note that the parties' extensive briefing on the pending motions contained several sub-arguments and cited to several cases not discussed above. I have reviewed those arguments and cases and conclude that they do not warrant further discussion as they do not affect the outcome of the pending motions.

For the reasons set forth above, I recommend that the pending motions to dismiss be DENIED:

1. The Court should deny Hikma's motion to dismiss the First Amended Complaint. (D.I. 19.)

2. The Court should deny Hikma's motion to dismiss the original Complaint as moot. (D.I. 11.)

3. The Court should deny Health Net's motion to dismiss the First Amended Complaint. (D.I. 30.)

This Report and Recommendation is filed pursuant to 28 U.S.C. § 636(b)(1)(B),(C), Federal Rule of Civil Procedure 72(b)(1), and District of Delaware Local Rule 72.1. Any objections to the Report and Recommendation shall be filed within fourteen days and limited to ten pages. Any response shall be filed within fourteen days thereafter and limited to ten pages. The failure of a party to object to legal conclusions may result in the loss of the right to *de novo* review in the district court.

The parties are directed to the Court's "Standing Order for Objections Filed Under Fed. R. Civ. P. 72," dated October 9, 2013, a copy of which can be found on the Court's website.

Dated: August 3, 2021

Jennifer L. Hall
UNITED STATES MAGISTRATE JUDGE

US009700537B2

(12) **United States Patent**
Yokoyama et al.

(10) **Patent No.: US 9,700,537 B2**
(45) **Date of Patent: *Jul. 11, 2017**

(54) **COMPOSITION FOR PREVENTING THE OCCURRENCE OF CARDIOVASCULAR EVENT IN MULTIPLE RISK PATIENT**

(71) Applicant: **MOCHIDA PHARMACEUTICAL CO., LTD.**, Tokyo (JP)

(72) Inventors: **Mitsuhiro Yokoyama**, Kobe (JP); **Hideki Origasa**, Toyama (JP); **Masunori Matsuzaki**, Ube (JP); **Yuji Matsuzawa**, Takarzuka (JP); **Yasushi Saito**, Chiba (JP)

(73) Assignee: **MOCHIDA PHARMACEUTICAL CO., LTD.**, Tokyo (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/431,958**

(22) Filed: **Feb. 14, 2017**

(65) **Prior Publication Data**

US 2017/0151206 A1 Jun. 1, 2017

Related U.S. Application Data

(62) Division of application No. 14/963,291, filed on Dec. 9, 2015, which is a division of application No. 14/474,955, filed on Sep. 2, 2014, now abandoned, which is a division of application No. 12/302,790, filed as application No. PCT/JP2007/061099 on May 31, 2007, now Pat. No. 8,853,256.

(30) **Foreign Application Priority Data**

May 31, 2006 (JP) 2006-152740

(51) **Int. Cl.**

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A61K 31/40	(2006.01)
A61K 31/366	(2006.01)
A61K 31/225	(2006.01)
A61K 31/202	(2006.01)
A61K 31/22	(2006.01)
A61K 31/351	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/22*** (2013.01); ***A61K 31/202*** (2013.01); ***A61K 31/225*** (2013.01); ***A61K 31/232*** (2013.01); ***A61K 31/351*** (2013.01); ***A61K 31/366*** (2013.01); ***A61K 31/40*** (2013.01); *A61K 2300/00* (2013.01)

(58) **Field of Classification Search**

USPC 514/560

See application file for complete search history.

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(74) *Attorney, Agent, or Firm* — Birch, Stewart, Kolasch & Birch, LLP

(57) **ABSTRACT**

Disclosed is a composition which is useful for preventing the occurrence of a cardiovascular event, particularly a composition which is expected to show a prophylactic effect on a cardiovascular event occurring in a hypercholesterolemia patient despite providing the patient with a treatment with HMG-CoA RI or a cardiovascular event occurring in a multiple risk patient.

16 Claims, 1 Drawing Sheet

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FIG. 1

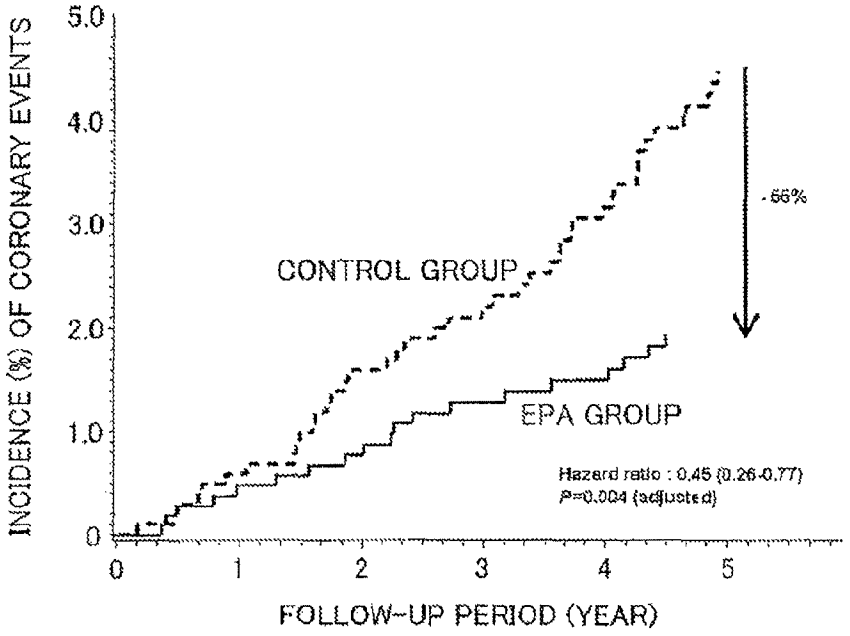
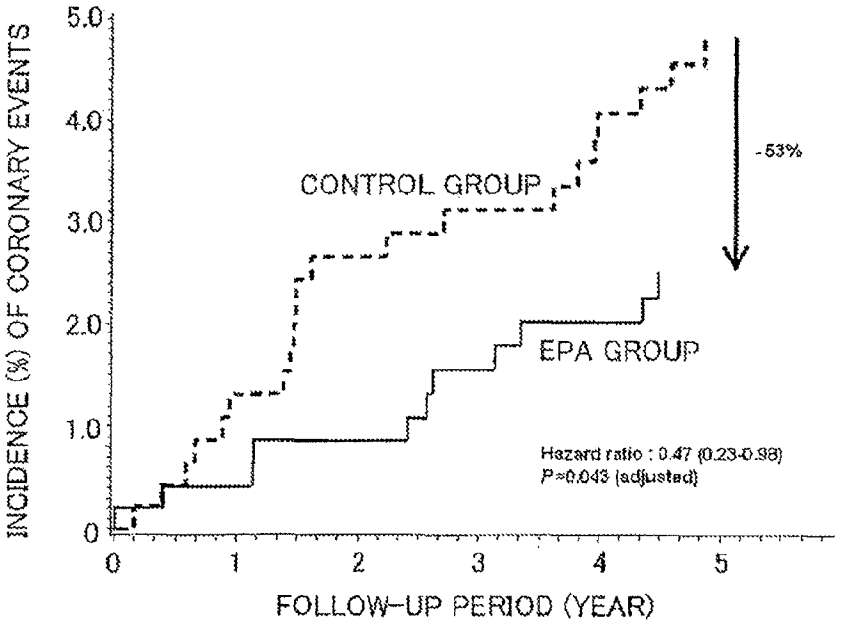

INCIDENCE (%) OF CORONARY EVENTS
5.0
4.0
3.0
2.0
1.0
0
CONTROL GROUP
EPA GROUP
-66%
Hazard ratio : 0.45 (0.26-0.77)
P=0.004 (adjusted)
0
1
2
3
4
5
FOLLOW-UP PERIOD (YEAR)

FIG. 2


INCIDENCE (%) OF CORONARY EVENTS
5.0
4.0
3.0
2.0
1.0
0
CONTROL GROUP
EPA GROUP
-53%
Hazard ratio : 0.47 (0.23-0.98)
P=0.043 (adjusted)
0
1
2
3
4
5
FOLLOW-UP PERIOD (YEAR)

COMPOSITION FOR PREVENTING THE OCCURRENCE OF CARDIOVASCULAR EVENT IN MULTIPLE RISK PATIENT

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a 37 C.F.R. §1.53(b) divisional of U.S. application Ser. No. 14/963,291 filed Dec. 9, 2015, which is a 37 C.F.R. §1.53(b) divisional of U.S. application Ser. No. 14/474,955 filed Sep. 2, 2014 (abandoned), which is a 37 C.F.R. §1.53(b) divisional of U.S. application Ser. No. 12/302,790 filed Nov. 26, 2008 (now U.S. Pat. No. 8,853,256 B2 issued Oct. 7, 2014), which is the National Phase of PCT International Application No. PCT/JP2007/061099 filed May 31, 2007, which in turn claims priority on Japanese Patent Application No. 2006-152740 filed May 31, 2006. The entire contents of each application is hereby incorporated by reference.

TECHNICAL FIELD

This invention relates to a composition for preventing occurrence of cardiovascular events (primary prevention) in multiple risk patients, the composition containing at least ethyl icosapentate (hereinafter abbreviated as EPA-E).

BACKGROUND ART

Westernization of diet has resulted in the increase of patients suffering from lifestyle-related diseases such as diabetes, hyperlipidemia, and hypertension. Some of these diseases finally lead to arteriosclerotic diseases such as myocardial infarction, angina pectoris, and cerebral infarction. Treatment of the lifestyle-related diseases is based on the improvement of lifestyle, and more specifically, on the alimentary therapy and kinesitherapy. However, such improvement of the dietary life or the lack of exercise is often difficult in the patients suffering from the "lifestyle-related diseases," and they usually transfer to pharmacotherapy in order to prevent poor prognosis, for example, onset of myocardial infarction or cerebral infarction.

An exemplary compound having the action of improving such lifestyle-related diseases is polyunsaturated fatty acid. The polyunsaturated fatty acid is defined as a fatty acid including two or more carbon-carbon double bonds in one molecule, and the polyunsaturated fatty acids are categorized by the position of the double bond into ω3 fatty acid, ω6 fatty acid, and the like. The ω3 polyunsaturated fatty acids include α-linolenic acid, icosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), and the ω6 polyunsaturated fatty acids include linoleic acid, γ-linolenic acid, and arachidonic acid. Polyunsaturated fatty acids are derived from natural products, and exhibit various actions including antiarteriosclerotic action, platelet aggregation inhibitory action, hypolipidemic action, antiinflammatory action, antitumor action, and central action, and due to the high safety, polyunsaturated fatty acids are incorporated in various kinds of food, or sold as a health food or drug.

Decrease in the death rate in the patients who have history of suffering from myocardial infarction has been reported for the administration of a mixture of ethyl ester of an ω-3 polyunsaturated fatty acid EPA (EPA-E) and ethyl ester of an ω-3 polyunsaturated fatty acid DHA (DHA-E) for 3.5 years (see Patent Document. 1). However, the results disclosed in Patent Document 1 relates to the secondary prevention, that is, prevention of recurrence, and the drug which is effective in the secondary prevention is not always effective in the primary prevention.

Based on the results of animal experiments and small scale clinical observations, many large scale clinical trials have been recently planned and conducted for the purpose of confirming whether various drugs which are effective in improving the lifestyle-related diseases can also prevent arteriosclerotic diseases in human. The results, however, have not necessarily been as intended, and the situation is still severe for the prevention of the occurrence of cardiovascular events in the case of patients suffering from a plurality of risk factors.

High purity EPA-E is commercially available in the trade names of Epadel™ and Epadel S™ (manufactured by Mochida Pharmaceutical Co., Ltd.) as therapeutic drugs for hyperlipidemia. There has been reported that when such high purity EPA-E is orally administered at 600 mg per administration and 3 times a day immediately after meal (when TG is abnormal, the dose is increased to the level of 900 mg per administration and 3 times a day), serum T-Cho concentration can be reduced by 3 to 6%, and serum TG can be reduced by 14 to 20% (see Non-Patent Document 1). There has also been reported in The Heart Failure Society of America 2005 Annual Meeting that, based on such action, such high purity EPA-E was expected to have the effects of improving cardiovascular events in hyperlipidemia patients, and combined use with HMG-CoA RI was effective in inhibiting cardiac events in a large scale clinical trial. In this large scale clinical trial (DELIS, Japan EPA Lipid Intervention Study), statistically significant suppression of the cardiac events by the EPA-E was confirmed for the total of the primary prevention patients and secondary prevention patients, and for the secondary prevention patients. On the other hand, in the analysis limited to the primary prevention patients, the incidence of the events was lower in the EPA-E group (the group administered with EPA-E in combination with HMG-CoA RI) compared to the control group (the group administered with solely with HMG-CoA RI), while this difference was not statistically significant. This trial also revealed that after 5 years from the start of the trial, the LDL-cholesterol value reduced by 26% in both of the EPA-E group and control group, that no significant difference was found between these groups, and that change of the HDL-cholesterol value was slight in both groups (see Non-Patent Document 2). This trial also revealed that the total cholesterol and the LDL-cholesterol decreased by 19% and 25%, respectively, in both the EPA-E group and the control group, and that triglyceride decreased by 9% (significant) and 4% in the EPA-E group and the control group, respectively, while little change in HDL-C was noted in both the EPA-E group and the control group (see Non-Patent Document 3). There is so far no report that has analyzed prevention of the occurrence of the cardiovascular events in the case of patients having two or more risk factors.

Patent Document 1: WO 00/48592 (JP 2002-537252 A)

Non-Patent Document 1: Drug Interview Form "EPA preparation, Epadel capsule 300", revised in July, 2002, and February, 2004, version 21 issued in December, 2004; pp. 21-22.

Non-Patent Document 2: Medical Tribune, issue of Nov. 17, 2005, Feature article 3, pp. 75-76.

Non-Patent Document 3: Lancet, vol. 369, pages 1090 to 1098 (2007).

DISCLOSURE OF THE INVENTION

Problems to be Solved by the Invention

In view of the situation that there is a serious problem that death from the cardiovascular disease is still a major cause of the death, and many cases of cardiovascular events are still impossible to prevent by the HMG-CoA RI therapy, an object of the present invention is to provide a composition for preventing onset of the cardiovascular events.

Means to Solve the Problems

In order to solve the problems as described above, the inventors of the present invention made an extensive study on a therapy of hypercholesterolemia patients and found that EPA-E has the effect of preventing occurrence of the cardiovascular events in patients suffering from multiple risk factors, and in particular, the effect of preventing occurrence of the cardiovascular events in male patients suffering from multiple risk factors. The present invention has been completed on the bases of such finding. Accordingly, the present invention is directed to the following:

(1) A composition for preventing occurrence of a cardiovascular event (primary prevention) in a hypercholesterolemia patient, the composition containing at least EPA-E as its effective component, wherein the patient also suffers from at least one risk factor selected from the group consisting of

(1) obesity,

(2) hypertension or prehypertension,

(3) diabetes, prediabetes, or abnormal glucose tolerance, and

(4) hypertriglyceridemia and/or low HDL cholesterolemia.

(2) A composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient, the composition containing at least EPA-E as its effective component, wherein the hypercholesterolemia patient is a patient also suffering from two or more of the risk factors.

(3) A composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient, the composition containing at least EPA-E as its effective component, wherein the patient also suffers from at least one of risk factors as defined by a body mass index (BMI) of at least 25 for the obesity; by a systolic blood pressure (SBP) of at least 140 mmHg or a diastolic blood pressure (DBP) of at least 90 mmHg for the hypertension or the prehypertension; by a fasting blood glucose (FBS) of at least 126 mg/dL or a hemoglobin Alc (HbAlc) of at least 6.5% for the diabetes, the prediabetes, or the abnormal glucose tolerance; and by triglyceride (TG) of at least 150 mg/dL and/or a HDL-C of less than 40 mg/dL for the hypertriglyceridemia and/or the low HDL cholesterolemia.

(4) The composition according to any one of (1) to (3) above, wherein the content of the EPA-E is at least 96.5% by weight in relation to the total content of fatty acid and derivatives thereof.

(5) The composition according to any one of (1) to (4) above, wherein the EPA-E is orally administered at a dose of 1.8 g/day to 2.7. g/day.

(6) The composition according to any one of (1) to (5) above, wherein the composition is used in combination with HMG-CoA RI.

(7) The composition according to any one of (1) to (6) above, wherein the hypercholesterolemia patient is a male patient.

(8) The composition according to any one of (1) to (7) above, wherein the hypercholesterolemia patient is a patient also suffering from hypertriglyceridemia and low HDL cholesterolemia.

(9) A method for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient by administering the patient with the composition according to any one of (1) to (8) above.

(10) Use of the composition according to any one of (1) to (8) above for the manufacture of an agent for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient.

Merits of the Invention

The above-mentioned composition of the present invention containing at least EPA-E as its effective component is effective in preventing occurrence of cardiovascular events in hypercholesterolemia patients, and in particular, in preventing occurrence of cardiovascular events in hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the risk of the cardiovascular events, or more particularly, in preventing occurrence of cardiovascular events in hypercholesterolemia patients also suffering from at least one risk factor selected from the group consisting of

(1) obesity,

(2) hypertension or prehypertension,

(3) diabetes, prediabetes, or abnormal glucose tolerance, and

(4) hypertriglyceridemia and/or low HDI, cholesterolemia.

The effect of the composition of the present Invention will be synergistically improved by combined use with the HMG-CoA RI, and such use of the composition of the present invention with the HMG-CoA RI has clinical utility since the effect of preventing the cardiovascular event occurrence is expected to be improved.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a graph prepared by plotting the incidence of the cardiovascular events in Y-axis and the time after the start of the trial in X-axis for male patients having at least 2 risk factors.

FIG. **2** is a graph prepared by plotting the incidence of the cardiovascular event in Y-axis and the time after the start of the trial in X-axis for patients having the risk factors of a triglyceride (TG) of at least 150 mg/dL and a HDL-C of less than 40 mg/dL.

BEST MODE FOR CARRYING OUT THE INVENTION

Next, the present invention is described in detail.

A first aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event (primary prevention) in a hypercholesterolemia patient, the composition containing at least EPA-E as its effective component, wherein the patient also suffers from at least one risk factor selected from the group consisting of

(1) obesity,

(2) hypertension or prehypertension,

(3) diabetes, prediabetes, or abnormal glucose tolerance, and

(4) hypertriglyceridemia and/or low HDL cholesterolemia.

Alternatively, the first aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event (primary prevention) in a hypercholesterolemia patient, the composition containing at least EPA-E and/or DHA-E as its effective component, wherein the patient also suffers from at least one risk factor selected from the group consisting of

(1) obesity,
(2) hypertension or prehypertension,
(3) diabetes, prediabetes, or abnormal glucose tolerance, and
(4) hypertriglyceridemia and/or low HDL cholesterolemia.

The prevention of the occurrence of the cardiovascular events include all cases of primary prevention, and exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest angina and exercise-induced angina, and destabilization of the angina. The composition of the present invention may be administered to any person who needs prevention of the occurrence of the cardiovascular events, and typical such patients are hypercholesterolemia patients.

A second aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient undergoing a HMG-CoA RI therapy, the composition containing at least EPA-E, wherein the patient also suffers from at least one risk factor selected from the group consisting of

(1) obesity,
(2) hypertension or prehypertension,
(3) diabetes, prediabetes, or abnormal glucose tolerance, and
(4) hypertriglyceridemia and/or low HDL cholesterolemia.

Alternatively, the second aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient undergoing a HMG-CoA RI therapy, the composition containing at least EPA-E and/or DHA-E, wherein the patient also suffers from at least one risk factor selected from the group consisting of

(1) obesity,
(2) hypertension or prehypertension,
(3) diabetes, prediabetes, or abnormal glucose tolerance, and
(4) hypertriglyceridemia and/or low HDL cholesterolemia.

While HMG-CoA RI includes all those having inhibitory action for 3-hydroxy-3-methylglutaryl coenzyme A reductase, the one used in the present invention is preferably a pharmaceutically administrable inhibitor which is preferably at least one member selected from the group consisting of pravastatin, simvastatin, lovastatin, fluvastatin, cerivastatin, atorvastatin, pitavastatin, rosuvastatin, and salts and derivatives thereof, and more preferably, pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin, pitavastatin, or rosuvastatin, and most preferably, pravastatin or simvastatin. All salts are included as long as they are pharmaceutically administrable, and preferred are sodium and calcium salts such as pravastatin sodium, fluvastatin sodium, cerivastatin sodium, atorvastatin calcium, pitavastatin calcium, and rosuvastatin calcium. In the present invention, "pravastatin," for example, also includes the pravastatin in the form of a salt unless otherwise noted.

A third aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient, the composition containing at least EPA-E as its effective component, wherein the patient also suffers from at least two risk factors selected from the group consisting of

(1) obesity,
(2) hypertension or prehypertension,
(3) diabetes, prediabetes, or abnormal glucose tolerance, and
(4) hypertriglyceridemia and/or low HDL cholesterolemia; namely; obesity, and hypertension or prehypertension; obesity, and diabetes, prediabetes, or abnormal glucose tolerance; obesity, and hypertriglyceridemia and/or low HDL cholesterolemia; hypertension or prehypertension, and diabetes, prediabetes or abnormal glucose tolerance; hypertension or prehypertension, and hypertriglyceridemia and/or low HDL cholesterolemia; diabetes, prediabetes, or abnormal glucose tolerance, and hypertriglyceridemia and/or low HDL cholesterolemia; obesity, and hypertension or prehypertension, and diabetes, prediabetes, or abnormal glucose tolerance; obesity, and hypertension or prehypertension, and hypertriglyceridemia and/or low HDL cholesterolemia; obesity, and diabetes, prediabetes, or abnormal glucose tolerance, and hypertriglyceridemia and/or low HDL cholesterolemia; hypertension or prehypertension, and diabetes, prediabetes, or abnormal glucose tolerance, and hypertriglyceridemia and/or low HDL cholesterolemia; obesity, and hypertension or prehypertension, and diabetes, prediabetes, or abnormal glucose tolerance, and hypertriglyceridemia and/or low HDL cholesterolemia.

Alternatively, the third aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient, the composition containing at least EPA-E and/or DHA-E as its effective component, wherein the patient also suffers from at least two risk factors selected from the group consisting of

(1) obesity,
(2) hypertension or prehypertension,
(3) diabetes, prediabetes, or abnormal glucose tolerance, and
(4) hypertriglyceridemia and/or low HDL cholesterolemia.

A fourth aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient, the composition containing at least EPA-E as its effective component, wherein the patient also suffers from at least one, and more preferably, at least two risk factors selected from the group consisting of

(1) obesity,
(2) hypertension or prehypertension,
(3) diabetes, prediabetes, or abnormal glucose tolerance, and
(4) hypertriglyceridemia and/or low HDL cholesterolemia. In this case, the hypercholesterolemia patient is preferably a male patient.

Alternatively, the fourth aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient, the composition containing at least EPA-E and/or DHA-E as its effective component, wherein the patient also suffers from at least one, and more preferably, at least two risk factors selected from the group consisting of

(1) obesity,
(2) hypertension or prehypertension,

(3) diabetes, prediabetes, or abnormal glucose tolerance, and

(4) hypertriglyceridemia and/or low HDL cholesterolemia. In this case, the hypercholesterolemia patient is preferably a male patient.

A fifth aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient, the composition containing at least EPA-E as its effective component, wherein the patient also suffers from risk factors of hypertriglyceridemia and low HDL cholesterolemia, and more specifically, hypertriglyceridemia and low HDL cholesterolemia with a serum triglyceride (TG) concentration of at least 150 mg/dl and a serum HDL-C concentration of less than 40 mg/dl, or serum TG/HDL-C ratio of at least 3.75. In this case, the hypercholesterolemia patient is preferably a male patient. Alternatively, the fifth aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event in a hypercholesterolemia patient, the composition containing at least EPA-E and/or DHA-E as its effective component, wherein the patient also suffers from risk factors of hypertriglyceridemia and low HDL cholesterolemia, and more specifically, hypertriglyceridemia and low HDL cholesterolemia with a serum triglyceride (TG) concentration of at least 150 mg/dl and a serum HDL-C concentration of less than 40 mg/dl, or a serum TG/HDL-C ratio of at least 3.75. In this case, the hypercholesterolemia patient is preferably a male patient.

A sixth aspect of the present invention provides a composition containing at least EPA-E as its effective component, the composition exhibiting an excellent effect of preventing occurrence of a cardiovascular event in a patient suffering from multiple risk factors who has been administered with this composition for at least 2 years since the start of the administration. Alternatively, the sixth aspect of the present invention provides a composition containing at least EPA-E and/or DHA-E as its effective component, the composition exhibiting an excellent effect of preventing recurrence of a cardiovascular event in a patient suffering from multiple risk factors who has been administered with this composition for at least 2 years since the start of the administration. The hypercholesterolemia patient is preferably a male patient.

A seventh aspect of the present invention provides a method for preventing occurrence of a cardiovascular event in a patient suffering from multiple risk factors by continuously administering the patient with a composition containing at least EPA-E as its effective component for at least 2 years. Alternatively, the seventh aspect of the present invention provides a method for preventing occurrence of a cardiovascular event in a patient suffering from multiple risk factors by continuously administering the patient with a composition containing at least EPA-E and/or DHA-E as its effective component for at least 2 years. The hypercholesterolemia patient is preferably a male patient.

An eighth aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event (primary prevention) in a dyslipidemia patient, the composition containing at least EPA-E as its effective component, wherein the patient also suffers from at least one risk factor selected from the group consisting of

(1) obesity,

(2) hypertension or prehypertension,

(3) diabetes, prediabetes, or abnormal glucose tolerance, and

(4) hypertriglyceridemia and/or low HDL cholesterolemia.

Alternatively, the eighth aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event (primary prevention) in a dyslipidemia patient, the composition containing at least EPA-E and/or DHA-E as its effective component, wherein the patient also suffers from at least one risk factor selected from the group consisting of

(1) obesity,

(2) hypertension or prehypertension,

(3) diabetes, prediabetes, or abnormal glucose tolerance, and

(4) hypertriglyceridemia and/or low HDL cholesterolemia.

A ninth aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event (primary prevention) in a hypercholesterolemia patient to be able to administered with HMG-CoA RI, the composition containing at least EPA-E as its effective component, wherein the patient also suffers from at least one risk factor selected from the group consisting of

(1) obesity,

(2) hypertension or prehypertension,

(3) diabetes, prediabetes, or abnormal glucose tolerance, and

(4) hypertriglyceridemia and/or low HDL cholesterolemia.

Alternatively, the ninth aspect of the present invention provides a composition for preventing occurrence of a cardiovascular event (primary prevention) in a hypercholesterolemia patient to be able to administered with HMG-CoA RI, the composition containing at least EPA-E and/or DHA-E as its effective component, wherein the patient also suffers from at least one risk factor selected from the group consisting of

(1) obesity,

(2) hypertension or prehypertension,

(3) diabetes, prediabetes, or abnormal glucose tolerance, and

(4) hypertriglyceridemia and/or low HDL cholesterolemia.

While the EPA-E content in the total fatty acid and dosage are not particularly limited as long as intended effects of the present invention are attained, the EPA-E used is preferably the one having a high purity, for example, the one having the proportion of the EPA-E in the total fatty acid and derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or higher, and still more preferably 96.5% by weight or higher. The daily dose in terms of EPA-E is typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more preferably 1.8 to 2.7 g/day. Another preferable daily dose is 0.3 to 2.7 g/day, and 0.3 to 1.8 g/day. Another preferable fatty acid included is DHA-E. While the compositional ratio of EPA-E/DHA-E, content of EPA-E and DHA-E (hereinafter referred to as (EPA-E+DHA-E)) in the total fatty acid, and dosage of (EPA-E+DHA-E) are not particularly limited as long as intended effects of the present invention are attained, the composition is preferably the one having a high purity of EPA-E and DHA-E, for example, the one having a proportion of the (EPA-E+DHA-E) in the total fatty acid and derivatives thereof of preferably 40% by weight or higher, more preferably 80% by weight or higher, and still more preferably 90% by weight or higher. The daily dose in terms of EPA-E+DHA-E is typically 0.3 to 10 g/day, preferably 0.5 to 6 g/day, and still more preferably 1 to 4 g/day. Another preferable daily dose is 0.3 to 6 g/day, 0.3 to 4 g/day, and 0.3 to 1 g/day. The content of other long chain saturated fatty acids is preferably low, and among the long

chain unsaturated fatty acids, the content of ω6 fatty acids, and in particular, the content of arachidonic acid is preferably as low as less than 2% by weight, and more preferably less than 1% by weight.

The composition of the present invention contains EPA-E and/or DHA-E, and has the effect of preventing occurrence of cardiovascular events in healthy people or those suffering from the risk factors of hyperlipidemia, diabetes, and hypertension when the composition is orally administered, and in particular, of preventing occurrence of cardiovascular events in hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffering from the risk of the cardiovascular events. The composition of the present invention may also be used in combination with the HMG-CoA RI, and such combination may further prevent the occurrence of the cardiovascular events.

The composition of the present invention may be used with other drugs, for example, antiplatelet drugs such as aspirin, ticlopidine, clopidogrel, prasugrel, and cilostazol; anticoagulants such as warfarin, heparin, and ximelagatran; antihypertensive drugs such as angiotensin II receptor antagonists (candesartan, losartan, valsartan, etc.), angiotensin converting enzyme inhibitors, calcium channel antagonists (amlodipine, cilnidipine, etc.), and al blockers; diabetes drugs or abnormal glucose tolerance stimulants such as α-glucosidase inhibitors (voglibose, acarbose, etc.), biguanide drugs, thiazolidinedione drugs (pioglitazone, rosiglitazone, rivoglitazone, etc.), and prompt insulin release promoters (mitiglinide, nateglinide, etc.); antilipotropic drugs and antiarteriosclerotic drugs such as HMG-CoA RI as described above, fibrate drugs, squalene synthetase inhibitors (TAK-475, etc.), and cholesterol absorption inhibitors (ezetimibe, etc.), probucol, anion exchange resin, nicotinic acid drugs, phytostero, elastase, dextran sulfate sodium sulfur, pantothenic acid, and polyenephosphatidylcholine.

The composition of the present invention contains smaller amounts of impurities such as saturated fatty acids and arachidonic acid which are unfavorable for cardiovascular events compared to fish oil or fish oil concentrate, and accordingly, the intended effects can be attained without causing problems like overnutrition or excessive intake of vitamin A. In addition, since the effective component of the present composition is in the form of an ester, the effective component is more stable to oxidation compared to the case of fish oil in which the effective component is in the form of a triglyceride, and a sufficiently stable composition can be produced by adding a conventional antioxidant. In other words, it is the use of the EPA-E that has for the first time enabled production of a composition for preventing onset of cardiovascular events which can be used in clinical practice.

In the present invention, the term "icosapentaenoic acid" designates all-cis-5,8,11,14,17-icosapentaenoic acid.

In the present invention, the term "hypercholesterolemia patient" means the patient with increased serum T-Cho concentration or serum LDL-Cho concentration. In a narrower sense, this term means the patient suffering from hypercholesterolemia (serum T-Cho concentration of at least about 220 mg/dl, and in more strict sense, at least 250 mg/dl) or high LDL cholesterolemia (serum LDL-Cho concentration of at least 140 mg/dL).

In the present invention, the term "dyslipidemia" is the condition which satisfies at least one of high LDL cholesterolemia (i.e. fasting serum LDL cholesterol value of at least 140 mg/dL), low HDL cholesterolemia (i.e. fasting serum HDL cholesterol value of less than 40 mg/dL), and hypertriglyceridemia (i.e. fasting serum triglyceride value of at least 150 mg/dL) according to the diagnostic criteria described in "Guideline for Preventing Arteriosclerotic diseases, 2007" (edited and published by Japan Atherosclerosis Society).

Of the risk factors treated in the present invention, "obesity" is the state with excessive accumulation of fats in the body. For example, non-limiting examples of the obesity include a body mass index (BMI) of at least 25, a waist measurement of at least 85 cm in male and at least 90 cm in female. "Hypertension" is the state with an abnormal increase in resting arterial blood pressure of the greater circulatory system. For example, in the criteria proposed by Japanese Society of Hypertension at the time of the filing of this application, hypertension is defined as a systolic blood pressure (SBP) of at least 140 mmHg or a diastolic blood pressure (DBP) of at least 90 mmHg. "Prehypertension" is the condition with the blood pressure between the normal blood pressure (or optimal blood pressure) and the blood pressure in the hypertension, and this condition is also referred to as "mild elevated blood pressure" or "borderline hypertension." Non-limiting exemplary criteria for such condition include a systolic blood pressure (SEP) of 120 to 139 mmHg or a diastolic blood pressure (DBP) of 80 to 89 mmHg. In the present invention, "hypertension or prehypertension" means a condition with a systolic blood pressure (SBP) of at least 120 mmHg or a diastolic blood pressure (DBP) of at least 80 mmHg, more strictly, a systolic blood pressure (SHP) of at least 135 mmHg or a diastolic blood pressure (DBP) of at least 85 mmHg, even more strictly a systolic blood pressure (SBP) of at least 140 mmHg or a diastolic blood pressure (DBP) of at least 90 mmHg. "Diabetes" is the glucose metabolism disorder caused by hyposecretion of insulin from the insulin-producing cell (β cell) in the pancreas or insufficient action of the insulin in the target cell. Exemplary non-limiting criteria proposed by Japan Diabetes Society at the time of the filing of this application is one of 1) fasting blood glucose of at least 126 mg/dL, 2) 75 g glucose tolerance test at 2 hours of at least 200 mg/dL, and 3) casual blood glucose level of at least 200 mg/dL; or a hemoglobin Alc (HbAlc) of at least 6.5%. The criteria, however, are not limited to these. "Prediabetes" is the condition in which the blood glucose level is between the normal value and the value in the diabetes. "Abnormal glucose tolerance" is the condition in which the blood glucose level in the glucose tolerance test is between the normal value and the value in the diabetes. These conditions are also referred to as the borderline diabetes, prediabetic state, and the diabetic high-risk group. For these conditions, exemplary non-limiting criteria include a fasting blood glucose of 110 to 125 mg/dL, a 75 g glucose tolerance test at 2 hours of 140 to 199 mg/dL, and a hemoglobin Alc (HbAlc) of 5.6 to 6.4%. In the present invention, "diabetes, prediabetes, or abnormal glucose tolerance" means a condition with a fasting blood glucose (FBS) of at least 110 mg/dL or a hemoglobin Alc (HbAlc) of at least 5.6%, more strictly, a fasting blood glucose (FBS) of at least 110 mg/dL or a hemoglobin Alc (HbAlc) of at least 5.9%, and even more strictly with a fasting blood glucose (FBS) of at least 126 mg/dL or a hemoglobin Alc (HbAlc) of at least 6.5%. "Hypertriglyceridemia" is the condition with an increased serum triglyceride (TG) concentration, and strictly, with the serum TG concentration of at least 150 mg/dL. "Low HDL cholesterolemia" is the condition with a reduced serum HDL-C concentration, and strictly, with the serum HDL-C concentration of less than 40 mg/dL. In the present invention, "hypertriglyceridemia and/or low HDL cholesterolemia" means the state with a serum TG concentration of at least 150 mg/dL and/or a serum HDL-C concentration of

less than 40 mg/dL. The hypertriglyceridemia and the low HDL cholesterolemia are both diseases included in the category of dyslipidemia, and they are mutually independent risk factors. Combination of these risk factors, however, is known to result in an increased risk of the occurrence of an arteriosclerotic disease. In the present invention, "the hypertriglyceridemia and/or the low HDL cholesterolemia" is treated as a single risk factor.

In the present invention, the term "combined use of EPA-E with HMG-CoA RI" include both the embodiment in which the EPA-E and the HMG-CoA RI are simultaneously administered and the embodiment in which both agents are separately administered. When these agents are simultaneously administered, they may be formulated either as a single combined drug or separate drugs. When these agents are separately administered, EPA-E may be administered either before or after the HMG-CoA RI. The doses and ratio of the EPA-E and the HMG-CoA RI may be adequately selected.

In the present invention, the term "combined use of EPA-E and/or DHA-E with HMG-CoA RI" include both the embodiment in which the EPA-E and/or DHA-E and the HMG-CoA RI are simultaneously administered and the embodiment in which these agents are separately administered. When these agents are simultaneously administered, they may be formulated either as a single combined drug or separate drugs. When these agents are separately administered, EPA-E and/or DHA-E may be administered either before or after the HMG-CoA RI. The doses and ratio of the EPA-E and/or DHA-E and the HMG-CoA RI may be adequately selected.

The composition of the present invention has the action of preventing onset of the cardiovascular events by the sole administration of the composition, and in particular, the present composition is expected to have the effect of preventing onset of the cardiovascular events which could not be prevented by the sole administration of the HMG-CoA RI. In addition, EPA-E has not only the action of reducing the serum T-Cho concentration and the serum TG, but also the action of suppressing platelet aggregation based on inhibition of arachidonic acid cascade, which is a pharmacological action different from the HMG-CoA RI. Therefore, the action as described above can also be exerted by combined administration with the HMG-CoA RI.

Since EPA-E and DHA-E are highly unsaturated, inclusion of an effective amount of an antioxidant such as butylated hydroxytoluene, butylated hydroxyanisole, propyl gallate, gallic acid, and pharmaceutically acceptable quinone, or α-tocopherol is preferable.

The preparation may be orally administered to the patient in the dosage form of tablet, capsule, microcapsule, granules, fine granules, powder, oral liquid preparation, syrup, or jelly. Preferably, the preparation is orally administered by filling in a capsule such as soft capsule or microcapsule.

The soft capsules containing high purity EPA-E (Epadel™ and Epadel S™) are commercially available in Japan as safe therapeutic agents for arteriosclerosis obliterans and hyperlipidemia with reduced side effects, and in such products, proportion of EPA-E in total fatty acid is at least 96.5% by weight. The soft capsule (Omacor™, Ross products, Reliant, and Pronova) containing about 46% by weight of EPA-E and about 38% by weight of DHA-E is commercially available in the U.S., Europe, and other countries as a drug applied for hypertriglyceridemia. These drugs may be purchased for use in the present invention.

The dose and administration period of the composition of the present invention for preventing the onset of the cardiovascular events is the dose and period sufficient for the expression of the intended action, and the dose and administration period may be adequately adjusted depending on the dosage form, administration route, daily frequency, severity of the symptoms, body weight, age, and the like. When orally administered, the composition may be administered at a dose in terms of EPA-E of 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and more preferably 1.8 to 2.7 g/day, and while such dose is typically administered in 3 divided doses, if desired, such dose may be administered in a single dose or in several divided doses. The composition is preferably administered during or after the meal, and more preferably, immediately (within 30 minutes) after the meal. When such dose is orally administered, the administration period is typically at least 1 year, preferably at least 2 years, more preferably at least 3 years and still more preferably at least 5 years. The administration, however, is preferably continued as long as there is a considerable risk of onset of the cardiovascular events. If necessary, drug holidays of about 1 day to 3 months, and preferably about 1 week to 1 month may be given.

The HMG-CoA RI is preferably used according to the dosage regimen recommended for the particular drug used, and the dose may be adequately adjusted depending on the type, dosage form, administration route, daily frequency, severity of the symptoms, body weight, gender, age, and the like. When orally administered, the HMG-CoA RI is typically administered at a dose of 0.05 to 200 mg/day, and preferably 0.1 to 100 mg/day in a single dose or in two divided doses. If necessary, the total dose may be administered in several divided doses. The dose of the HMG-CoA RI may be reduced depending on the dose of the EPA-E.

It is to be noted that pravastatin sodium (Mevalotin™ tablets and fine granules, Daiichi Sankyo Co., Ltd.), simvastatin (Lipovas™ tablets, Banyu Pharmaceutical Co., Ltd.), fluvastatin sodium (Lochol™ Tablets, Novartis Pharma K.K. and Tanabe Seiyaku Co., Ltd.), atorvastatin calcium hydrate (Lipitor™ tablets, Astellas Pharma Inc. and Pfizer Inc.), pitavastatin calcium (Livalo™, Kowa Company, Ltd. and Daiichi Sankyo Co., Ltd.), and rosuvastatin calcium (Crestor™ tablets, AstraZeneca and Shionogi & Co., Ltd.) are commercially available in Japan as drugs for treating hyperlipidemia, and lovastatin (Mevacor™ tablets, Merck) is commercially available in the U.S. as a drug for treating hyperlipidemia. These drugs may be purchased and used according to the prescribed dosing schedules.

In the case of pravastatin sodium, the preferable daily dose is 5 to 60 mg, and more preferably 10 to 20 mg, and in the case of simvastatin, the preferable daily dose is 2.5 to 60 mg, and more preferably 5 to 20 mg. In the case of fluvastatin sodium, the preferable daily dose is 10 to 180 mg, and more preferably 20 to 60 mg, and in the case of atorvastatin calcium hydrate, the preferable daily dose is 5 to 120 mg, and more preferably 10 to 40 mg. In the case of pitavastatin calcium, the preferable daily dose is 0.5 to 12 mg, and more preferably 1 to 4 mg, and in the case of rosuvastatin calcium, the preferable daily dose is 1.25 to 60 mg, and more preferably 2.5 to 20 mg. in the case of lovastatin, the preferable daily dose is 5 to 160 mg, and more preferably 10 to 80 mg, and in the case of cerivastatin sodium, the preferable daily dose is 0.075 to 0.9 mg, and more preferably 0.15 to 0.3 mg. The dose, however, is not limited to those as described above.

EXAMPLES

Next, the effects of the composition of the present invention are demonstrated by referring to Examples, which by no means limit the scope of the present invention.

Example 1: Effect of the EPA-E in Preventing Occurrence of Cardiovascular Events in Patients Having Multiple Risk Factors

Trial Procedure

This trial corresponds to a partial analysis of the results obtained in JELIS (Japan EPA Lipid Intervention Study) which is a large scale clinical trial of high purity EPA preparation which was presented in The Heart Failure Society of America 2005 Annual Meeting (for general information on JELIS, see Medical Tribune, issue of Nov. 17, 2005, Feature article 3, pp. 75-76).

More specifically, for the EPA-E group (7503 cases) and the control group (7478 cases) evaluated for the primary prevention effect in the 18,645 subject patients of the DELIS trial (EPA-E group (9,326 cases) and control group (9,319 cases)), occurrence of the cardiovascular events was observed and analysed for 5 years from the start of the administration in relation to the number of risk factors at the registration as defined by the following (1) to (4):

(1) obesity: body mass index (BMI) of at least 25;

(2) hypertension or prehypertension: systolic blood pressure (SBP) of at least 140 mmHg or diastolic blood pressure (DBP) of at least 90 mmHg;

(3) diabetes, prediabetes, or abnormal glucose tolerance: fasting blood glucose (FBS) of at least 126 mg/dL or hemoglobin Alc (HbAlc) of at least 6.5%;

(4) hypertriglyceridemia or low HDL cholesterolemia: a triglyceride (TG) of at least 150 mg/dL or a HDL-C of less than 40 mg/dL.

The EPA-E group was orally administered with Epadel (Mochida Pharmaceutical Co., Ltd.) typically at an adult dose of 600 mg per administration and 3 times a day after the meal. However, in the case of abnormal serum TG, the dose could be increased to 900 mg per administration and 3 times a day. In both groups, pravastatin sodium (Mevalotin™ tablets and fine granules, Daiichi Sankyo Co., Ltd.), simvastatin (Lipovas™ tablets, Banyu Pharmaceutical Co., Ltd.), or atorvastatin calcium hydrate (Lipitor™ tablets, Astellas Pharma Inc. and Pfizer Inc.) was used for the base drug, and these drugs were orally administered according to the prescribed dosage regimen. More specifically, pravastatin sodium was orally administered at a daily dose of 10 to 20 mg in a single dose or two divided doses; simvastatin was orally administered at a daily dose of 5 to 20 mg in a single dose; atorvastatin calcium hydrate was orally administered at a daily dose of 10 to 40 mg in a single dose.

Results

The number of occurrence of cardiovascular events in the observation period of 5 years, incidence (%), and rate of suppression of the incidence of the cardiovascular events in the EPA-E group with respect to the control group are shown in Table 1 for each number of risk factors. The rate of suppression of the incidence of the cardiovascular events was calculated by the formula: [{(incidence in the control group)−(incidence in the EPA-E group)}/incidence in the control group]×100.

TABLE 1

Number of risk factors	Incidence in the control group (cases of occurrence/ all cases, %)	Incidence in the EPA-E group (cases of occurrence/ all cases, %)	Rate of Suppression (%)
0	14/1309 (1.1)	11/1326 (0.8)	22
1	29/2424 (1.2)	25/2468 (1.0)	15
2	46/2324 (2.0)	34/2238 (1.5)	23
3	29/1205 (2.4)	28/1229 (2.3)	5
4	9/216 (4.2)	6/242 (2.5)	40
1-2	75/4748 (1.6)	59/4706 (1.3)	21
1-3	104/5953 (1.7)	87/5935 (1.5)	18
1-4	113/6169 (1.8)	93/6177 (1.5)	18
2-3	75/3529 (2.1)	62/3467 (1.8)	16
2-4	84/3745 (2.2)	68/3709 (1.8)	18
3-4	38/1421 (2.7)	34/1471 (2.3)	14

The incidence (%) of cardiovascular events was found to increase with the increase in the number of risk factors. While the incidence was 1.1% for the risk factor number of 0 and 4.2% for the risk factor number 4 in the control group, the incidence was 0.8% in the risk factor number 0 and 2.5% for the case of risk factor number 4 in the group administered with the EPA-E. As evident from Table 1, for all cases of both groups with 1 to 4 risk factors, the cardiovascular event incidence was lower in the group administered with the EPA-E compared to the control group, and the cardiovascular events were suppressed by 5 to 40%. The effect of preventing occurrence of the cardiovascular events by the administration of the EPA-E was thereby confirmed for the hypercholesterolemia patients having the risk factors.

From the results of the trial as described above, the number of occurrence of cardiovascular events in the observation period of 5 years, incidence (%), and rate of suppression of the incidence of the cardiovascular events in the EPA-E group with respect to the control group were calculated for the male patients having at least two risk factors. The results are shown in Table 2. (The calculation was conducted by the same procedure as described above.)

TABLE 2

Number of risk factors	Incidence in the control group (cases of occurrence/ all cases, %)	Incidence in the EPA-E group (cases of occurrence/ all cases, %)	Rate of Suppression (%)
2-4	43/1053 (4.1)	19/1065 (1.8)	56

FIG. **1** is a graph prepared by plotting the incidence of the cardiovascular events in Y-axis and time after the start of the trial in X-axis.

As evident from Table 2 and FIG. **1**, in the case of male patients having two or more risk factors, EPA-E significantly suppressed the occurrence of cardiovascular events. It was also confirmed that decrease in the incidence of the cardiovascular events was significant after 2 years or more from

the start of the administration. At the end of the trial, the rate of suppression of the cardiovascular event occurrence was 56% compared to the control group (the value after correcting the dispersion between groups was 55%; see FIG. **1**).

From the results of the trial as described above, the number of occurrence of cardiovascular events in the observation period of 5 years, incidence (%), and rate of suppression of the incidence of the cardiovascular events in the EPA-E group with respect to the control group were calculated for the patients exhibiting a triglyceride (TG) of at least 150 mg/dL and a HDL-C of less than 40 mg/dL as the risk factors. The results are shown in Table 3. (The calculation was conducted by the same procedure as described above.)

TABLE 3

Risk factor	Incidence in the control group (cases of occurrence/ all cases, %)	Incidence in the EPA-E group (cases of occurrence/ all cases, %)	Rate of Suppression (%)
TG of at least 150 mg/dL and HDL-C of less than 40 mg/dL	21/475 (4.4)	11/482 (2.3)	48

FIG. **2** is a graph prepared by plotting the incidence of the cardiovascular events in Y-axis and time after the start of the trial in X-axis.

As evident from Table 3 and FIG. **2**, EPA-E significantly suppressed occurrence of cardiovascular events in the patients having the risk factors of the triglyceride (TG) of at least 150 mg/dL and the HDL-C of less than 40 mg/dL. It was also confirmed that decrease in the incidence of the cardiovascular events was significant after 2 years or more from the start of the administration. At the end of the trial, the rate of suppression of the cardiovascular event occurrence was 48% compared to the control group (the value after correcting the dispersion between groups was 53%; see FIG. **2**). This suggests that the composition containing EPA-E as its effective component effectively prevents the occurrence of the cardiovascular event in the patient having the serum TG/HDL-C ratio of at least 3.75. It is also to be noted that, while the events that occurred in the control group were fatal myocardial infarction, nonfatal myocardial infarction, new occurrence of angina and cardiovascular angioplasty, the events that occurred in the EPA-E group were either nonfatal myocardial infarction or new occurrence of angina, and occurrence of fatal events was not found in the EPA-E group.

In addition, in the group of patients having the risk factor of the triglyceride of at least 150 mg/dL, the occurrence of the cardiovascular events was suppressed by 15% in the EPA-E group compared to the control group; and in the group of patients having the risk factor of HDL-C of less than 40 mg/dL, the occurrence of the cardiovascular events was suppressed by 35% compared to the control group (both values are uncorrected values).

As described above, a significant effect of the EPA-E administration was confirmed for the prevention of the occurrence of the cardiovascular events in the hypercholesterolemia patients having the risk factors.

What is claimed:

1. A method of reducing occurrence of a cardiovascular event in a hypercholesterolemia patient consisting of:

identifying a patient having triglycerides (TG) of at least 150 mg/DL and HDL-C of less than 40 mg/dL in a blood sample taken from the patient as a risk factor of a cardiovascular event, wherein the patient has not previously had a cardiovascular event, and administering ethyl icosapentate in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor,

wherein said 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitor is administered to the patient at least one of before, during and after administering the ethyl icosapentate; and

wherein the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor is selected from the group consisting of pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin, pitavastatin, rosuvastatin, and salts thereof, and

wherein daily dose of the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor are 5 to 60 mg for pravastatin, 2.5 to 60 mg for simvastatin, 10 to 180 mg for fluvastatin sodium, 5 to 120 mg for atorvastatin calcium hydrate, 0.5 to 12 mg for pitavastatin calcium, 1.25 to 60 mg for rosuvastatin calcium, 5 to 160 mg for lovastatin, and 0.075 to 0.9 mg for cerivastatin sodium.

2. The method according to claim **1**, wherein the ethyl icosapentate is orally administered at a dose of 1.8 g/day to 2.7 g/day.

3. The method according to claim **1**, wherein the hypercholesterolemia patient is a male patient.

4. The method according to claim **1**, wherein the ethyl icosapentate is administered daily for two years or more.

5. The method according to claim **1**, wherein the cardiovascular event is a fatal cardiovascular event.

6. The method according to claim **1**, wherein the hypercholesterolemia patient has a serum [triglyceride (TG)/ HDL-C] ratio of at least 3.75.

7. The method according to claim **1**, wherein the ethyl icosapentate is orally administered at a dose of 0.3 g/day to 6 g/day.

8. The method according to claim **1**, wherein the content of the ethyl icosapentate is at least 96.5% by weight in relation to the total content of fatty acid that is simultaneously administered with the ethyl icosapentate.

9. A method of reducing occurrence of a cardiovascular event in a hypercholesterolemia patient consisting of:

identifying a patient having (i) total cholesterol (TC) of at least 220 mg/dL or LDL-cholesterol (LDL-C) of at least 140 mg/dL, and (ii) triglycerides (TG) of at least 150 mg/dL and HDL-C of less than 40 mg/dL in a blood sample taken from the patient as a risk factors of a cardiovascular event, wherein the patient has not previously had a cardiovascular event, and

administering ethyl icosapentate in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor,

wherein said 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitor is administered to the patient at least one of before, during and after administering the ethyl icosapentate; and

wherein the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor is selected from the group consisting of pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin, pitavastatin, rosuvastatin, and salts thereof, and

wherein daily dose of the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor are 5 to 60 mg for pravastatin, 2.5 to 60 mg for simvastatin, 10 to 180 mg for fluvastatin sodium, 5 to 120 mg for atorvastatin calcium hydrate, 0.5 to 12 mg for pitavastatin calcium,

1.25 to 60 mg for rosuvastatin calcium, 5 to 160 mg for lovastatin, and 0.075 to 0.9 mg for cerivastatin sodium.

10. The method according to claim **9**, wherein the ethyl icosapentate is orally administered at a dose of 1.8 g/day to 2.7 g/day.

11. The method according to claim **9**, wherein the hypercholesterolemia patient is a male patient.

12. The method according to claim **9**, wherein the ethyl icosapentate is administered daily for two years or more.

13. The method according to claim **9**, wherein the cardiovascular event is a fatal cardiovascular event.

14. The method according to claim **9**, wherein the hypercholesterolemia patient has a serum [triglyceride (TG)/HDL-C] ratio of at least 3.75.

15. The method according to claim **9**, wherein the ethyl icosapentate is orally administered at a dose of 0.3 g/day to 6 g/day.

16. The method according to claim **9**, wherein the content of the ethyl icosapentate is at least 96.5% by weight in relation to the total content of fatty acid that is simultaneously administered with the ethyl icosapentate.

* * * * *

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(12) **United States Patent**
Soni

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(54) **METHODS OF REDUCING THE RISK OF A CARDIOVASCULAR EVENT IN A SUBJECT AT RISK FOR CARDIOVASCULAR DISEASE**

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(60) Division of application No. 16/502,621, filed on Jul. 3, 2019, which is a continuation of application No. 16/287,157, filed on Feb. 27, 2019, now Pat. No. 10,383,840, which is a continuation of application No. 16/005,852, filed on Jun. 12, 2018, now Pat. No. 10,278,935, which is a continuation of application No. 15/886,422, filed on Feb. 1, 2018, now Pat. No. 10,016,386, which is a continuation of application No. 15/607,084, filed on May 26, 2017, now Pat. No. 9,918,955, which is a continuation of application No. 15/427,238, filed on Feb. 8, 2017, now Pat. No. 9,693,986, which is a continuation of application No. 15/333,991, filed on Oct. 25, 2016, now Pat. No. 9,610,272, which is a continuation of application No. 14/411,815, filed as application No. PCT/US2013/048559 on Jun. 28, 2013, now Pat. No. 9,603,826.

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(57) **ABSTRACT**

In various embodiments, the present invention provides methods of reducing the risk of a cardiovascular event in a subject on statin therapy and, in particular, a method of reducing the risk of a cardiovascular event in a subject on statin therapy having a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL, and administering to the subject a pharmaceutical composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester or a derivative thereof.

7 Claims, No Drawings

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METHODS OF REDUCING THE RISK OF A CARDIOVASCULAR EVENT IN A SUBJECT AT RISK FOR CARDIOVASCULAR DISEASE

PRIORITY CLAIM

This application is a divisional of U.S. patent application Ser. No. 16/502,621 filed Jul. 3, 2019, which is a continuation of U.S. patent application Ser. No. 16/287,157 filed Feb. 27, 2019 (now U.S. Pat. No. 10,383,840), which is a continuation of U.S. patent application Ser. No. 16/005,852 filed Jun. 12, 2018 (now U.S. Pat. No. 10,278,935), which is a continuation of U.S. patent application Ser. No. 15/886,422 filed Feb. 1, 2018 (now U.S. Pat. No. 10,016,386), which is a continuation application of U.S. patent application Ser. No. 15/607,084 filed May 26, 2017 (now U.S. Pat. No. 9,918,955), which is a continuation of U.S. patent application Ser. No. 15/427,238 filed Feb. 8, 2017 (now U.S. Pat. No. 9,693,986), which is a continuation application of U.S. patent application Ser. No. 15,333,991 filed Oct. 25, 2016 (now U.S. Pat. No. 9,610,272), which is a continuation of U.S. patent application Ser. No. 14/411,815, filed Dec. 29, 2014 (now U.S. Pat. No. 9,603,826), which is a 371 national stage application of PCT/US2013/048559 filed Jun. 28, 2013, and which claims priority to U.S. provisional patent application Ser. No. 61/666,447, filed Jun. 29, 2012, the entire contents of which are incorporated herein by reference.

BACKGROUND

Cardiovascular disease is one of the leading causes of death in the United States and most European countries. It is estimated that over 70 million people in the United States alone suffer from a cardiovascular disease or disorder including but not limited to high blood pressure, coronary heart disease, dyslipidemia, congestive heart failure and stroke.

Lovaza®, a lipid regulating agent, is indicated as an adjunct to diet to reduce triglyceride levels in adult patients with very high triglyceride levels. Unfortunately, Lovaza® can significantly increase LDL-C and/or non-HDL-C levels in some patients. A need exists for improved treatments for cardiovascular diseases and disorders.

SUMMARY

In various embodiments, the present invention provides methods of reducing the risk of a cardiovascular event in a subject on statin therapy. In one embodiment, the method comprises administering to the subject a pharmaceutical composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester or a derivative thereof. In another embodiment, the subject has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL. In another embodiment, the composition contains not more than 10%, by weight, docosahexaenoic acid or derivative thereof, substantially no docosahexaenoic acid or derivative thereof, or no docosahexaenoic acid or derivative thereof. In another embodiment, eicosapentaenoic acid ethyl ester comprises at least 96%, by weight, of all fatty acids present in the composition; the composition contains not more than 4%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; and/or the composition contains about 0.1% to about 0.6% of at least one fatty acid other than eicosapentaenoic acid ethyl ester and docosahexaenoic acid.

In another embodiment, the invention provides a method of treating hypertriglyceridemia comprising administering a composition as described herein to a subject in need thereof one to about four times per day.

These and other embodiments of the present invention will be disclosed in further detail herein below.

DETAILED DESCRIPTION

While the present invention is capable of being embodied in various forms, the description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the invention, and is not intended to limit the invention to the specific embodiments illustrated. Headings are provided for convenience only and are not to be construed to limit the invention in any manner. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

The use of numerical values in the various quantitative values specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about." Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values recited as well as any ranges that can be formed by such values. Also disclosed herein are any and all ratios (and ranges of any such ratios) that can be formed by dividing a disclosed numeric value into any other disclosed numeric value. Accordingly, the skilled person will appreciate that many such ratios, ranges, and ranges of ratios can be unambiguously derived from the numerical values presented herein and in all instances such ratios, ranges, and ranges of ratios represent various embodiments of the present invention.

Compositions

In one embodiment, a composition of the invention is administered to a subject in an amount sufficient to provide a daily dose of eicosapentaenoic acid of about 1 mg to about 10,000 mg, 25 about 5000 mg, about 50 to about 3000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about

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In one embodiment, a composition for use in methods of the invention comprises eicosapentaenoic acid, or a pharmaceutically acceptable ester, derivative, conjugate or salt thereof, or mixtures of any of the foregoing, collectively referred to herein as "EPA." The term "pharmaceutically acceptable" in the present context means that the substance in question does not produce unacceptable toxicity to the subject or interaction with other components of the composition.

In another embodiment, the EPA comprises an eicosapentaenoic acid ester. In another embodiment, the EPA comprises a C_1-C_5 alkyl ester of eicosapentaenoic acid. In another embodiment, the EPA comprises eicosapentaenoic acid ethyl ester, eicosapentaenoic acid methyl ester, eicosapentaenoic acid propyl ester, or eicosapentaenoic acid butyl ester.

In another embodiment, the EPA is in the form of ethyl-EPA, lithium EPA, mono-, di- or triglyceride EPA or any other ester or salt of EPA, or the free acid form of EPA. The EPA may also be in the form of a 2-substituted derivative or other derivative which slows down its rate of oxidation but does not otherwise change its biological action to any substantial degree.

In another embodiment, EPA is present in a composition useful in accordance with methods of the invention in an amount of about 50 mg to about 5000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225

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In another embodiment, a composition useful in accordance with the invention contains not more than about 10%, not more than about 9%, not more than about 8%, not more than about 7%, not more than about 6%, not more than about 5%, not more than about 4%, not more than about 3%, not more than about 2%, not more than about 1%, or not more than about 0.5%, by weight, docosahexaenoic acid (DHA), if any. In another embodiment, a composition of the invention contains substantially no docosahexaenoic acid. In still another embodiment, a composition useful in the present invention contains no docosahexaenoic acid and/or derivative thereof.

In another embodiment, EPA comprises at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%, by weight, of all fatty acids present in a composition that is useful in methods of the present invention.

In some embodiments, the composition comprises at least 96% by weight of eicosapentaenoic acid ethyl ester and less than about 2% by weight of a preservative. In some embodiments, the preservative is a tocopherol such as all-racemic α-tocopherol.

In another embodiment, a composition useful in accordance with methods of the invention contains less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5% or less than 0.25%, by weight of the total composition or by weight of the total fatty acid content, of any fatty acid other than EPA. Illustrative examples of a "fatty acid other than EPA" include linolenic acid (LA), arachidonic acid (AA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), stearadonic acid (STA), eicosatrienoic acid (ETA) and/or docosapentaenoic acid (DPA). In another embodiment, a composition useful in accordance with methods of the invention contains about 0.1% to about 4%, about 0.5% to about 3%, or about 1% to about 2%, by weight, of total fatty acids other than EPA and/or DHA.

In another embodiment, a composition useful in accordance with the invention has one or more of the following features: (a) eicosapentaenoic acid ethyl ester represents at least about 96%, at least about 97%, or at least about 98%, by weight, of all fatty acids present in the composition; (b) the composition contains not more than about 4%, not more than about 3%, or not more than about 2%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; (c) the composition contains not more than about 0.6%, not more than about 0.5%, or not more than about 0.4% of any individual fatty acid other than eicosapentaenoic acid ethyl ester; (d) the composition has a refractive index (20° C.) of about 1 to about 2, about 1.2 to about 1.8 or about 1.4 to about 1.5; (e) the composition has a specific gravity (20° C.) of about 0.8 to about 1.0, about 0.85 to about 0.95 or about 0.9 to about 0.92; (e) the composition contains not more than about 20 ppm, not more than about 15 ppm or not more than about 10 ppm heavy metals, (f) the composition contains not more than about 5 ppm, not more than about 4 ppm, not more than about 3 ppm, or not more than about 2 ppm arsenic, and/or (g) the composition has a peroxide value of not more than about 5 meq/kg, not more than about 4 meq/kg, not more than about 3 meq/kg, or not more than about 2 meq/kg.

In another embodiment, compositions useful in accordance with methods of the invention are orally deliverable. The terms "orally deliverable" or "oral administration" herein include any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is swallowed. Thus "oral administration" includes buccal and sublingual as well as esophageal administration. In one embodiment, the composition is present in a capsule, for example a soft gelatin capsule.

A composition for use in accordance with the invention can be formulated as one or more dosage units. The terms "dose unit" and "dosage unit" herein refer to a portion of a pharmaceutical composition that contains an amount of a therapeutic agent suitable for a single administration to provide a therapeutic effect. Such dosage units may be administered one to a plurality (i.e. 1 to about 10, 1 to 8, 1 to 6, 1 to 4 or 1 to 2) of times per day, or as many times as needed to elicit a therapeutic response.

In one embodiment, compositions of the invention, upon storage in a closed container maintained at room temperature, refrigerated (e.g. about 5 to about 5-10° C.) temperature, or frozen for a period of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, exhibit at least about 90%, at least about 95%, at least about 97.5%, or at least about 99% of the active ingredient(s) originally present therein.

Therapeutic Methods

In one embodiment, the invention provides a method for treatment and/or prevention of cardiovascular-related disease and disorders. The term "cardiovascular-related disease and disorders" herein refers to any disease or disorder of the heart or blood vessels (i.e. arteries and veins) or any symptom thereof. Non-limiting examples of cardiovascular-related disease and disorders include hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia, coronary heart disease, vascular disease, stroke, atherosclerosis, arrhythmia, hypertension, myocardial infarction, and other cardiovascular events.

The term "treatment" in relation a given disease or disorder, includes, but is not limited to, inhibiting the disease

or disorder, for example, arresting the development of the disease or disorder; relieving the disease or disorder, for example, causing regression of the disease or disorder; or relieving a condition caused by or resulting from the disease or disorder, for example, relieving, preventing or treating symptoms of the disease or disorder. The term "prevention" in relation to a given disease or disorder means: preventing the onset of disease development if none had occurred, preventing the disease or disorder from occurring in a subject that may be predisposed to the disorder or disease but has not yet been diagnosed as having the disorder or disease, and/or preventing further disease/disorder development if already present.

In various embodiments, the present invention provides methods of reducing a risk of a cardiovascular event in a subject on statin therapy. In some embodiments, the method comprises (a) identifying a subject on statin therapy and having a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL, wherein said subject has established cardiovascular disease or has a high risk of developing cardiovascular disease; and (b) administering to the subject a pharmaceutical composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester per day, wherein the composition contains substantially no docosahexaenoic acid.

In some embodiments, the subject has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL, for example 135 mg/dL to 500 mg/dL, 150 mg/dL to 500 mg/dL, or 200 mg/dL to <500 mg/dL. In some embodiments, the subject or subject group has a baseline triglyceride level (or median baseline triglyceride level in the case of a subject group), fed or fasting, of about 135 mg/dL, about 140 mg/dL, about 145 mg/dL, about 150 mg/dL, about 155 mg/dL, about 160 mg/dL, about 165 mg/dL, about 170 mg/dL, about 175 mg/dL, about 180 mg/dL, about 185 mg/dL, about 190 mg/dL, about 195 mg/dL, about 200 mg/dL, about 205 mg/dL, about 210 mg/dL, about 215 mg/dL, about 220 mg/dL, about 225 mg/dL, about 230 mg/dL, about 235 mg/dL, about 240 mg/dL, about 245 mg/dL, about 250 mg/dL, about 255 mg/dL, about 260 mg/dL, about 265 mg/dL, about 270 mg/dL, about 275 mg/dL, about 280 mg/dL, about 285 mg/dL, about 290 mg/dL, about 295 mg/dL, about 300 mg/dL, about 305 mg/dL, about 310 mg/dL, about 315 mg/dL, about 320 mg/dL, about 325 mg/dL, about 330 mg/dL, about 335 mg/dL, about 340 mg/dL, about 345 mg/dL, about 350 mg/dL, about 355 mg/dL, about 360 mg/dL, about 365 mg/dL, about 370 mg/dL, about 375 mg/dL, about 380 mg/dL, about 385 mg/dL, about 390 mg/dL, about 395 mg/dL, about 400 mg/dL, about 405 mg/dL, about 410 mg/dL, about 415 mg/dL, about 420 mg/dL, about 425 mg/dL, about 430 mg/dL, about 435 mg/dL, about 440 mg/dL, about 445 mg/dL, about 450 mg/dL, about 455 mg/dL, about 460 mg/dL, about 465 mg/dL, about 470 mg/dL, about 475 mg/dL, about 480 mg/dL, about 485 mg/dL, about 490 mg/dL, about 495 mg/dL, or about 500 mg/dL.

In some embodiments, the subject or subject group is also on stable therapy with a statin (with or without ezetimibe). In some embodiments, the subject or subject group also has established cardiovascular disease, or is at high risk for establishing cardiovascular disease. In some embodiments, the subject's statin therapy includes administration of one or more statins. For example and without limitation, the subject's statin therapy may include one or more of: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. In some embodiments, the subject is additionally administered one or more of: amlodipine, ezetimibe, niacin, and sitagliptin. In some embodiments, the subject's statin therapy includes administration of a statin and ezetimibe. In some embodiments, the subject's statin therapy includes administration of a statin without ezetimibe.

In some embodiments, the subject's statin therapy does not include administration of 200 mg or more per day of niacin and/or fibrates. In some embodiments, the subject is not on concomitant omega-3 fatty acid therapy (e.g., is not being administered or co-administered a prescription and/or over-the-counter composition comprising an omega-3 fatty acid active agent). In some embodiments, the subject is not administered or does not ingest a dietary supplement comprising an omega-3 fatty acid.

In some embodiments, the subject has established cardiovascular disease ("CV disease" or "CVD"). The status of a subject as having CV disease can be determined by any suitable method known to those skilled in the art. In some embodiments, a subject is identified as having established CV disease by the presence of any one of: documented coronary artery disease, documented cerebrovascular disease, documented carotid disease, documented peripheral arterial disease, or combinations thereof. In some embodiments, a subject is identified as having CV disease if the subject is at least 45 years old and: (a) has one or more stenosis of greater than 50% in two major epicardial coronary arteries; (b) has had a documented prior MI; (c) has been hospitalized for high-risk NSTE ACS with objective evidence of ischemia (e.g., ST-segment deviation and/or biomarker positivity); (d) has a documented prior ischemic stroke; (e) has symptomatic artery disease with at least 50% carotid arterial stenosis; (0 has asymptomatic carotid artery disease with at least 70% carotid arterial stenosis per angiography or duplex ultrasound; (g) has an ankle-brachial index ("ABI") of less than 0.9 with symptoms of intermittent claudication; and/or (h) has a history of aorto-iliac or peripheral arterial intervention (catheter-based or surgical).

In some embodiments, the subject or subject group being treated in accordance with methods of the invention has a high risk for developing CV disease. For example and without limitation, a subject or subject group has a high risk for developing CV disease if the subject or subject in a subject group is age 50 or older, has diabetes mellitus (Type 1 or Type 2), and at least one of: (a) is a male age 55 or older or a female age 65 or older; (b) is a cigarette smoker or was a cigarette smoker who stopped less than 3 months prior; (c) has hypertension (e.g., a blood pressure of 140 mmHg systolic or higher, or greater than 90 mmHg diastolic); (d) has an HDL-C level of ≤40 mg/dL for men or ≤50 mg/dL for women; (e) has an hs-CRP level of >3.0 mg/L; (0 has renal dysfunction (e.g., a creatinine clearance ("CrCL") of greater than 30 mL/min and less than 60 mL/min); (g) has retinopathy (e.g., defined as any of: non-proliferative retinopathy, preproliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease, or history of photocoagulation); (h) has microalbuminuria (e.g., a positive micral or other strip test, an albumin/creatinine ratio of ≥2.5 mg/mmol, or an albumin excretion rate on timed collection of ≥20 mg/min all on at least two successive occasions); (i) has macroalbuminuria (e.g., albumix or other dip stick evidence of gross proteinuria, an albumin/creatinine ratio of ≥25 mg/mmol, or an albumin excretion rate on timed collection of ≥200 mg/min all on at least two successive occasions); and/or (j) has an ankle-brachial index of <0.9 without symptoms of intermittent claudication.

In some embodiments, the subject's baseline lipid profile is measured or determined prior to administering the pharmaceutical composition to the subject. Lipid profile characteristics can be determined by any suitable method known to those skilled in the art including, for example, by testing a fasting or non-fasting blood sample obtained from the subject using standard blood lipid profile assays. In some embodiments, the subject has one or more of: a baseline non-HDL-C value of about 200 mg/dL to about 300 mg/dL; a baseline total cholesterol value of about 250 mg/dL to about 300 mg/dL; a baseline VLDL-C value of about 140 mg/dL to about 200 mg/dL; a baseline HDL-C value of about 10 to about 30 mg/dL; and/or a baseline LDL-C value of about 40 to about 100 mg/dL.

In some embodiments, the cardiovascular event for which risk is reduced is one or more of: cardiovascular death; nonfatal myocardial infarction; nonfatal stroke; coronary revascularization; unstable angina (e.g., unstable angina determined to be caused by myocardial ischemia by, for example, invasive or non-invasive testing, and requiring hospitalization); cardiac arrest; peripheral cardiovascular disease requiring intervention, angioplasty, bypass surgery or aneurysm repair; death; and onset of new congestive heart failure.

In some embodiments, the subject is administered about 1 g to about 4 g of the pharmaceutical composition per day for about 4 months, about 1 year, about 2 years, about 3 years, about 4 years, about 5 years, or more than about 5 years. Thereafter, in some embodiments the subject exhibits one or more of

(a) reduced triglyceride levels compared to baseline;

(b) reduced Apo B levels compared to baseline;

(c) increased HDL-C levels compared to baseline;

(d) no increase in LDL-C levels compared to baseline;

(e) a reduction in LDL-C levels compared to baseline;

(f) a reduction in non-HDL-C levels compared to baseline;

(g) a reduction in VLDL levels compared to baseline;

(h) a reduction in total cholesterol levels compared to baseline;

(i) a reduction in high sensitivity C-reactive protein (hs-CRP) levels compared to baseline; and/or

(j) a reduction in high sensitivity troponin (hsTnT) levels compared to baseline.

In some embodiments, the subject exhibits one or more of: (a) a reduction in triglyceride level of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 55% as compared to baseline;

(b) a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in non-HDL-C levels or a reduction in non-HDL-C levels of at least about 1%, at least about 3%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50% as compared to baseline;

(c) an increase in HDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50% as compared to baseline; and/or

(d) a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in LDL-C levels or a reduction in LDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 55% as compared to baseline.

In one embodiment, the subject or subject group being treated has a baseline EPA blood level on a (mol %) basis of less than 2.6, less than 2.5, less than 2.4, less than 2.3, less than 2.2, less than 2.1, less than 2, less than 1.9, less than 1.8, less than 1.7, less than 1.6, less than 1.5, less than 1.4, less than 1.3, less than 1.2, less than 1.1 or less than 1.

In another embodiment, the subject or subject group being treated has a baseline triglyceride level (or median baseline triglyceride level in the case of a subject group), fed or fasting, of about 135 mg/dL to about In some embodiments, the subject or subject group being treated in accordance with methods of the invention is on stable therapy with a statin (with or without ezetimibe). As used herein, the phrase "on stable therapy with a statin" means that the subject or subject group has been on the same daily dose of the same statin for at least 28 days and, if applicable, the same daily dose of ezetimibe for at least 28 days. In some embodiments, the subject or subject group on stable statin therapy has an LDL-C level of about 40 mg/dL to about 100 mg/dL.

In some embodiments, safety laboratory tests of subject blood samples include one or more of: hematology with complete blood count ("CBC"), including RBC, hemoglobin (Hgb), hematocrit (Hct), white cell blood count (WBC), white cell differential, and platelet count; and biochemistry panel including total protein, albumin, alkaline phosphatase, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), total bilirubin, glucose, calcium, electrolytes, (sodium, potassium, chloride), blood urea nitrogen (BUN), serum creatinine, uric acid, creatine kinase, and HbA_{1c}.

In some embodiments, a fasting lipid panel associated with a subject includes TG, TC, LDL-C, HDL-C, non-HDL-C, and VLDL-C. In some embodiments, LDL-C is calculated using the Friedewald equation, or is measured by preparative ultracentrifugation (Beta Quant) if the subject's triglyceride level is greater than 400 mg/dL. In some embodiments, LDL-C is measured by ultracentrifugation (Beta Quant) at randomization and again after about one year after randomization.

In some embodiments, a biomarker assay associated with blood obtained from a subject includes hs-CRP, Apo B and hsTnT.

In some embodiments, a medical history associated with a subject includes family history, details regarding all illnesses and allergies including, for example, date(s) of onset, current status of condition(s), and smoking and alcohol use.

In some embodiments, demographic information associated with a subject includes day, month and year of birth, race, and gender.

In some embodiments, vital signs associated with a subject include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (e.g., oral body temperature).

In some embodiments, a physical examination of a subject includes assessments of the subject's general appearance, skin, head, neck, heart, lung, abdomen, extremities, and neuromusculature.

In some embodiments, the subject's height and weight are measured. In some embodiments, the subject's weight is recorded with the subject wearing indoor clothing, with shoes removed, and with the subject's bladder empty.

In some embodiments, a waist measurement associated with the subject is measured. In some embodiments, the

waist measurement is determined with a tape measure at the top of the subject's hip bone.

In some embodiments, an electrocardiogram associated with the subject is obtained. In some embodiments, an ECG is obtained every year during the treatment/follow-up portion of the study. In some embodiments, the ECG is a 12-lead ECG. In some embodiments, the ECG is analyzed for detection of silent MI.

In some embodiments, subjects randomly assigned to the treatment group receive 4 g per day of a composition comprising at least 96% by weight of eicosapentaenoic acid ethyl ester. In some embodiments, the composition is encapsulated in a gelatin capsule. In some embodiments, subjects in this treatment group continue to take 4 g per day of the composition for about 1 year, about 2 years, about 3 years, about 4 years, about 4.75 years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, about 10 years, or more than about 10 years. In some embodiments, a median treatment duration is planned to be about 4 years.

In some embodiments, the present invention provides a method of reducing a risk of cardiovascular events in a subject. In some embodiments, the method comprises administering to the subject a composition comprising at least 96% by weight of eicosapentaenoic acid ethyl ester. In some embodiments, the subject is administered about 1 g to about 4 g of the composition per day.

In some embodiments, the reduced risk of CV events is indicated or determined by comparing an amount of time (e.g., an average amount of time) associated with a subject or subject group from first dosing to a first CV event selected from the group consisting of: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization (e.g., emergent hospitalization) for unstable angina determined to be caused by myocardial ischemia (e.g., by invasive or non-invasive testing), to an amount of time (e.g., an average amount of time) associated with a placebo or untreated subject or group of subjects from first dosing with a placebo to a first CV event selected from the group consisting of: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization (e.g., emergent hospitalization) for unstable angina determined to be caused by myocardial ischemia (e.g., by invasive or non-invasive testing), wherein said placebo does not include eicosapentaenoic acid ethyl ester. In some embodiments, the amount of time associated with the subject or group of subjects are compared to the amount of time associated with the placebo or untreated subject or group of subjects are compared using a log-rank test. In some embodiments, the log-rank test includes one or more stratification factors such as CV Risk Category, use of ezetimibe, and/or geographical region.

In some embodiments, the present invention provides a method of reducing risk of CV death in a subject on stable statin therapy and having CV disease or at high risk for developing CV disease, comprising administering to the subject a composition as disclosed herein.

In another embodiment, the present invention provides a method of reducing risk of recurrent nonfatal myocardial infarction (including silent MI) in a subject on stable statin therapy and having CV disease or at high risk for developing CV disease, comprising administering to the patient one or more compositions as disclosed herein.

In some embodiments, the present invention provides a method of reducing risk of nonfatal stroke in a subject on stable statin therapy and having CV disease or at high risk for developing CV disease, comprising administering to the subject a composition as disclosed herein.

In some embodiments, the present invention provides a method of reducing risk of coronary revascularization in a subject on stable statin therapy and having CV disease or at high risk for developing CV disease, comprising administering to the subject a composition as disclosed herein.

In some embodiments, the present invention provides a method of reducing risk of developing unstable angina caused by myocardial ischemia in a subject on stable statin therapy and having CV disease or at high risk for developing CV disease, comprising administering to the subject a composition as disclosed herein.

In another embodiment, any of the methods disclosed herein are used in treatment or prevention of a subject or subjects that consume a traditional Western diet. In one embodiment, the methods of the invention include a step of identifying a subject as a Western diet consumer or prudent diet consumer and then treating the subject if the subject is deemed a Western diet consumer. The term "Western diet" herein refers generally to a typical diet consisting of, by percentage of total calories, about 45% to about 50% carbohydrate, about 35% to about 40% fat, and about 10% to about 15% protein. A Western diet may alternately or additionally be characterized by relatively high intakes of red and processed meats, sweets, refined grains, and desserts, for example more than 50%, more than 60% or more or 70% of total calories come from these sources.

In another embodiment, a composition as described herein is administered to a subject once or twice per day. In another embodiment, 1, 2, 3 or 4 capsules, each containing about 1 g of a composition as described herein, are administered to a subject daily. In another embodiment, 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the morning, for example between about 5 am and about 11 am, and 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the evening, for example between about 5 pm and about 11 pm.

In some embodiments, the risk of a cardiovascular event in a subject is reduced compared to a control population. In some embodiments, a plurality of control subjects to a control population, wherein each control subject is on stable statin therapy, has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL, and has established cardiovascular disease or a high risk of developing cardiovascular disease, and wherein the control subjects are not administered the pharmaceutical composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester per day.

In some embodiments, a first time interval beginning at (a) an initial administration of a composition as disclosed herein to the subject to (b) a first cardiovascular event of the subject is greater than or substantially greater than a first control time interval beginning at (a') initial administration of a placebo to the control subjects to (b') a first cardiovascular event in the control subjects. In some embodiments, the first cardiovascular event of the subject is a major cardiovascular event selected from the group consisting of: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina caused by myocardial ischemia. In some embodiments, the first cardiovascular event of the control subjects is a major cardiovascular event selected from the group consisting of: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina caused by myocardial ischemia. In some embodiments, the first cardiovascular event of the subject and the first cardio-

vascular event of the control subjects is any of: death (from any cause), nonfatal myocardial infarction, or nonfatal stroke. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: death from a cardiovascular cause, nonfatal myocardial infarction, coronary revascularization, unstable angina, peripheral cardiovascular disease, or cardiac arrhythmia requiring hospitalization. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: death from a cardiovascular cause, nonfatal myocardial infarction, and coronary revascularization, unstable angina. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: death from a cardiovascular cause and nonfatal myocardial infarction. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is death (from any cause). In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: fatal myocardial infarction and nonfatal myocardial infarction (optionally including silent MI). In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is coronary revascularization. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is hospitalization (e.g. emergent hospitalization) for unstable angina (optionally unstable angina caused by myocardial ischemia). In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any one of: fatal stroke or nonfatal stroke. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any one of: new coronary heart failure, new coronary heart failure leading to hospitalization, transient ischemic attack, amputation for coronary vascular disease, and carotid revascularization. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any one of: elective coronary revascularization and emergent coronary revascularization. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is an onset of diabetes. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is cardiac arrhythmia requiring hospitalization. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is cardiac arrest.

In some embodiments, a second time interval beginning at (a) an initial administration of the pharmaceutical composition to the subject to (c) a second cardiovascular event of the subject is greater than or substantially greater than a second control time interval beginning at (a') initial administration of a placebo to the control subjects to (c') a second cardiovascular event in the control subjects. In some embodiments, the second cardiovascular event of the subject and the second cardiovascular event of the control subjects is a major cardiovascular event selected from the group consisting of: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina caused by myocardial ischemia.

In some embodiments, the subject has diabetes mellitus and the control subjects each have diabetes mellitus. In some embodiments, the subject has metabolic syndrome and the control subjects each have metabolic syndrome.

In some embodiments, the subject exhibits one or more of (a) reduced triglyceride levels compared to the control population; (b) reduced Apo B levels compared to the control population; (c) increased HDL-C levels compared to the control population; (d) no increase in LDL-C levels compared to the control population; (e) a reduction in LDL-C levels compared to the control population; (f) a reduction in non-HDL-C levels compared to the control population; (g) a reduction in VLDL levels compared to the control population; (h) a reduction in total cholesterol levels compared to the control population; (i) a reduction in high sensitivity C-reactive protein (hs-CRP) levels compared to the control population; and/or (j) a reduction in high sensitivity troponin (hsTnT) levels compared to the control population.

In some embodiments, the subject's weight after administration of the composition is less than a baseline weight determined before administration of the composition. In some embodiments, the subject's waist circumference after administration of the composition is less than a baseline waist circumference determined before administration of the composition.

In methods of the present invention in which a time interval is determined or assessed, the time interval may be for example an average, a median, or a mean time interval. For example, in embodiments wherein a first control time interval is associated with a plurality of control subjects, the first control time interval is an average, a median, or a mean of a plurality of first control time intervals associated with each control subject. Similarly, in embodiments wherein a second control time interval is associated with a plurality of control subjects, the second control time interval is an average, a median, or a mean of a plurality of second control time intervals associated with each control subject.

In some embodiments, the reduced risk of cardiovascular events is expressed as a difference in incident rates between a study group and a control population. In some embodiments, the subjects in the study group experience a first major cardiovascular event after an initial administration of a composition as disclosed herein at a first incidence rate which is less than a second incidence rate, wherein the second incidence rate is associated with the rate of cardiovascular events in the subjects in the control population. In some embodiments, the first major cardiovascular event is any one of: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina (optionally determined to be caused by myocardial ischemia). In some embodiments, the first and second incidence rates are determined for a time period beginning on the date of the initial administration and ending about 4 months, about 1 year, about 2 years, about 3 years, about 4 years, or about 5 years after the date of initial administration.

In another embodiment, the invention provides use of any composition described herein for treating hypertriglyceridemia in a subject in need thereof, comprising: providing a subject having a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL and administering to the subject a pharmaceutical composition as described herein. In one embodiment, the composition comprises about 1 g to about 4 g of eicosapentaenoic acid ethyl ester, wherein the composition contains substantially no docosahexaenoic acid.

EXAMPLES

A phase 3, multi-center, placebo-controlled randomized, double-blind, 12-week study with an open-label extension is

performed to evaluate the efficacy and safety of AMR101 in patients with fasting triglyceride levels≥150 mg/dL and <500 mg/dL. The primary objective is, in patients at LDL-C goal while on statin therapy, with established cardiovascular disease (CVD) or at high risk for CVD, and hypertriglyceridemia (fasting triglycerides, TG, ≥200 mg/dL and <500 mg/dL, determine the efficacy of AMR101 4 g daily, compared to placebo, in preventing the occurrence of a first major cardiovascular event of the composite endpoint that includes:

- cardiovascular ("CV") death;
- nonfatal myocardial infarction ("MI");
- nonfatal stroke;
- coronary revascularization; and
- unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emertgent hospitalization.

The secondary objectives of this study are the following:

To evaluate the effect of therapy on the composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or peripheral CV disease requiring intervention, angioplasty, bypass surgery, and aneurysm repair;

To evaluate the effect of therapy on combinations of each of the clinical events listed in secondary objective #1, supra, in addition to cardiac arrhythmia requiring hospitalization, cardiac arrest, peripheral CV disease requiring intervention, angioplasty, bypass surgery, aneurysm repair, and total mortality;

To evaluate the effect of therapy on the occurrence of a second, third, fourth and fifth major cardiovascular event (e.g., occurrence of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization after a first occurrence of any of same);

To evaluate the effect of therapy on the first occurrence of a major cardiovascular event in subgroups of patients including (a) those with diabetes mellitus, and (b) those with metabolic syndrome (e.g., as defined by the NCEP ATP III or future criteria as may evolve therefrom);

To evaluate the effect of therapy on new congestive heart failure ("CHF"), on new CHF as a primary cause of hospitalization, on transient ischemic attack, on amputation for CV disease, and on carotid revascularization;

To evaluate the effect of therapy on occurrence of elective coronary revascularization and emergent coronary revascularization;

To evaluate the effects of therapy on lipids, lipoproteins and inflammatory markers including triglycerides, total cholesterol, low-density lipoprotein cholesterol ("LDL-C"), high-density lipoprotein cholesterol ("HDL-C"), non-HDL-C, very low-density lipoprotein cholesterol ("VLDL-C"), apoliporpotein B ("apo B"), high-sensitivity C-reactive protein ("hs-CRP"), and high-sensitivity troponin ("hsTnT") as follows:

Evaluation of the effect of therapy on each marker;

Evaluation of the effect of the baseline value of each marker on therapy effects; and

Evaluation of the effect of therapy for preventing clinical events as defined above among all patients in the study and in sub-groups such as patients with diabetes mellitus and patients with substantial on-treatment changes of any of the markers;

To evaluate the effect of therapy on new onset diabetes; and

To explore the effect of therapy on weight and waist circumference.

Study Population

The population for this study is men and women≥45 years of age with established CVD, or men and women≥50 years of age with diabetes in combination with one additional risk factor for CVD. In addition, all patients will have atherogenic dyslipidemia defined as on treatment for hypercholesterolemia (but at treatment goal for LDL-C, by treatment with a statin) and hypertriglyceridemia. More details are listed in the inclusion criteria.

The patients will need to provide consent to participate in the study and be willing and able to comply with the protocol and the study procedures.

Study Periods

This study consists of the following study periods:

Screening Period: During the screening period, patients will be evaluated for inclusion/exclusion criteria.

At the first visit to the Research Unit (Visit 1), study procedures will be performed for evaluation of patient's eligibility in the study. At this screening visit, patients will sign an informed consent form before any study procedure is performed; the informed consent form will cover the treatment/follow-up period. Based on the evaluation from Visit 1, the following situations may occur:

Patients who are eligible for participation based on the study procedures on Visit 1 will return to the Research Unit for Visit 2 (randomization visit) to start the treatment/follow-up period. This case includes, for example, patients at Visit lwho are on a stable dose of a statin, are planning to stay on the same statin and the same dose of the statin, and who not need to wash out any non-statin lipid-altering medications.

Patients who are not eligible for participation based on the study procedures on Visit 1 and are unlikely to become eligible in the next 28 days (for example: unlikely to stabilize statin dose, unable to wash out non-statin lipid-altering medications, etc.): these patients will be screen failed after Visit 1.

Patients not eligible for participation in the study based on the study procedures on Visit 1 may possibly become eligible in the next 28 days: these patients may return at the discretion of the investigator for a second optional screening visit (Visit 1.1) at which time the procedures needed for re-evaluation of the previously failed inclusion/exclusion criteria will be repeated. This case includes, for example, patients who are started on a statin at Visit 1, whose statin dose is changed at Visit 1, and/or needed to wash out non-statin lipid-altering medications. The following applies for these patients:

Patients with a change in the statin or statin dose on Visit 1 will need to be on a stable statin dose for at least 28 days before the lipid qualifying measurements at Visit 1.1. Other concomitant medications (antidiabetic therapy, for example) can be optimized or stabilized during this period.

Patients starting a washout at Visit 1 will have a washout period of at least 28 days (only 7 days for bile acid sequestrants) before the lipid qualifying measurements at Visit 1.1.

Patients at Visit 1 who are on a stable dose of a statin, are planning to stay on the same statin at the same dose, and who do not need any medication washout, but were asked to return for Visit 1.1 to repeat one or more of the other study procedures not related to concomitant medications

Patients who become eligible for participation based on the additional study procedures at Visit 1.1 will return to the Research Unit for Visit 2 (randomization visit) to start the treatment/follow-up period.

At the end of the screening period, patients will need to meet all inclusion/exclusion criteria before they can be randomized. Patients who are not eligible for participation after the screening period (based on study procedures at Visit 1 and/or Visit 1.1) may return at a later date for rescreening. These patients will need to re-start with all procedures starting with Visit 1. This includes patients who need more time to stabilize one or more conditions or therapies (for example: statin, antidiabetic, antihypertensive, thyroid hormone, HIV-protease inhibitor therapy).

Treatment/Follow-Up Period: Within 42 days after the first screening visit (Visit 1) or within 60 days after the first screening visit (Visit 1) for those patients that have a second screening visit (Visit 1.1), eligible patients will enter the treatment/follow-up period. During this period, the patients will receive study drug during the planned visits at the Research Site and take the study drug while away from the Research Site.

During the visits, study procedures will be performed for evaluation of efficacy and safety. A detailed schedule of procedures is provided in Table 1.

Study Duration

The estimated study duration includes a planned 18-month enrollment period followed by a follow-up period of approximately 3.5 years in expected duration (approximately 5 years in total). Patients will be randomized at different times during the enrollment period but will all end the study at the same date (study end date). It is planned that all randomized patients will receive study medication and be followed-up until the study end date. This is an event-driven trial and patients will continue in the trial if the trial runs longer than expected, or will terminate earlier if the trial runs shorter than expected.

The total duration of the trial is based on a median 4-year follow-up period across patients. The first patient randomized would be followed for 4.75 years (the longest individual follow-up duration), and the last patient randomized would be followed for 3.25 year (the shortest individual follow-up duration).

Study Groups

At Visit 2 (Day 0), eligible study patients will be randomly assigned to the following treatment groups:

Group 1: AMR101 4 g daily (four 1000 mg capsules daily)

Group 2: placebo (four capsules daily)

The four AMR101 or placebo capsules daily will be taken as two capsules in the morning and two capsules in the evening (twice-per-day dosing regimen).

Number of Patients

This is an event-driven trial: It is expected that a minimum of 1612 primary efficacy endpoint events will be required during the study. A total of approximately 7990 patients will be entered into the study to either receive AMR101 or placebo (approximately 3995 patients per treatment group) in order to observe an estimated 1612 events that make up the primary composite endpoint for efficacy.

Number of Study Sites

Participants will be enrolled at multiple Research Sites in multiple countries.

Randomization

On Day 0, eligible patients will be randomized to one of 2 study groups using a computer-generated randomization schema. Randomized treatment assignment to either AMR101 or placebo in a 1:1 ratio will be provided using the internet (IWR).

Blinding

This is a double-blind study. Patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and personnel at the organization(s) and vendors supporting the study will be unaware of the randomization code (i.e., they will not know which study participants are receiving the experimental drug and which are receiving the placebo drug). The study medication AMR101 and placebo capsules will be similar in size and appearance to maintain blinding.

During the double-blind treatment/follow-up period, everyone (patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and personnel at the organization(s) and vendors managing/supporting the study), with the exception of the laboratory personnel performing the analysis, will be blinded to individual results of the efficacy laboratory measurements (including lipid values). Individual results from the lipid profile may be unblinded in the event of an emergency for a patient.

Stratification

Participants will be assigned to treatment groups stratified by CV risk category, use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries). There are two CV risk categories:

CV Risk Category 1: patients with established CVD defined in the inclusion criteria. Patients with diabetes and established CVD are included in this category.

CV Risk Category 2: patients with diabetes and at least one additional risk factor for CVD, but no established CVD.

Stratification will be recorded in the IWR at the time of enrollment. Approximately 70% of randomized patients will be in the CV Risk Category 1 and approximately 30% of randomized patients will be in the CV Risk Category 2. Enrollment with patients of a CV risk category will be stopped when the planned number of patients in that risk category is reached.

Study Population

Inclusion Criteria

Patients meeting the following criteria will be eligible to participate in the study:

Fasting TG levels of ≥200 mg/dL (2.26 mmol/L) and <500 mg/dL (5.64 mmol/L).

LDL-C>40 mg/dL (1.04 mmol/L) and ≤100 mg/dL (2.60 mmol/L) and on stable therapy with a statin (with or without ezetimibe) for at least 4 weeks prior to the LDL-C/TG baseline qualifying measurements for randomization

Stable therapy is defined as the same daily dose of the same statin for at least 28 days before the lipid qualification measurements (TG and LDL-C) and, if applicable, the same daily dose of ezetimibe for at least 28 days before the lipid qualification measurements (TG and LDL-C). Patients who have their statin therapy or use of ezetimibe initiated at Visit 1, or have their statin, statin dose and/or ezetimibe dose changed at Visit 1, will need to go through a stabilization period of at least 28 days since initiation/change and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).

Statins may be administered with or without ezetimibe.

If patients qualify at the first qualification visit (Visit 1) for TG and LDL-C, and meet all other inclusion/exclusion criteria, they may be randomized at Visit 2. If patients don't qualify at the first qualifying visit (Visit 1), a second

re-qualifying visit (Visit 1.1) is allowed. For some patients, because they need to stabilize medications and/or need to washout medications, the second re-qualifying visit (Visit 1.1) will be needed after the stabilization/washout period.

Either having established CVD (in CV Risk Category 1) or at high risk for CVD (in CV Risk Category 2). The CV risk categories are defined as follows:

CV Risk Category 1: defined as men and women≥45 years of age with one or more of the following:

Documented coronary artery disease (CAD; one or more of the following primary criteria must be satisfied):

Documented multivessel CAD (>50% stenosis in at least two major epicardial coronary arteries—with or without antecedent revascularization)

Documented prior MI

Hospitalization for high-risk NSTE-ACS (with objective evidence of ischemia: ST-segment deviation or biomarker positivity)

Documented cerebrovascular or carotid disease (one of the following primary criteria must be satisfied):

Documented prior ischemic stroke

Symptomatic carotid artery disease with ≥50% carotid arterial stenosis

Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis per angiography or duplex ultrasound

History of carotid revascularization (catheter-based or surgical)

Documented peripheral arterial disease (PAD; one or more of the following primary criteria must be satisfied):

ABI<0.9 with symptoms of intermittent claudication

History of aorto-iliac or peripheral arterial intervention (catheter-based or surgical)

OR

CV Risk Category 2: defined as patients with:

Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication AND

Men and women≥50 years of age AND

One of the following at Visit 1 (additional risk factor for CVD):

Men≥55 years of age or women≥65 years of age;

Cigarette smoker or stopped smoking within 3 months before Visit 1;

Hypertension (blood pressure≥140 mmHg systolic OR≥90 mmHg diastolic) or on antihypertensive medication;

HDL-C≤40 mg/dL for men or ≤50 mg/dL for women;

Hs-CRP>3.00 mg/L (0.3 mg/dL);

Renal dysfunction: CrCL>30 and <60 mL/min (>0.50 and <1.00 mL/sec);

Retinopathy, defined as any of the following: non-proliferative retinopathy, preproliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease or a history of photocoagulation;

Micro- or macroalbuminuria. Microalbuminuria is defined as either a positive micral or other strip test (may be obtained from medical records), an albumin creatinine ratio≥2.5 mg/mmol or an albumin excretion rate on timed collection≥20 mg/min all on at least two successive occasions; macroalbuminuria, defined as albustix or other dipstick evidence of gross proteinuria, an albumin:creatinine ratio≥25 mg/mmol or an albumin excretion rate on timed collection≥200 mg/min all on at least two successive occasions;

ABI<0.9 without symptoms of intermittent claudication (patients with ABI<0.9 with symptoms of intermittent claudication are counted under CV Risk Category 1).

Patients with diabetes with CVD as defined above are eligible based on the CVD requirements and will be counted under CV Risk Category 1. Only patients with diabetes and no documented CVD as defined above need at least one additional risk factor as listed, and will be counted under CV Risk Category 2.

Women may be enrolled if all 3 of the following criteria are met:

They are not pregnant;

They are not breastfeeding;

They do not plan on becoming pregnant during the study.

Women of child-bearing potential must have a negative urine pregnancy test before randomization.

Women are not considered to be of childbearing potential if they meet one of the following criteria as documented by the investigator:

They have had a hysterectomy, tubal ligation or bilateral oophorectomy prior to signing the informed consent form;

They are post-menopausal, defined as ≥1 year since their last menstrual period or have a follicle-stimulating hormone (FSH) level in a menopausal range.

Women of childbearing potential must agree to use an acceptable method of avoiding pregnancy from screening to the end of the study, unless their sexual partner(s) is/are surgically sterile or the woman is abstinent.

Understanding of the study procedures, willing to adhere to the study schedules, and agreement to participate in the study by giving informed consent prior to screening.

Agree to follow a physician recommended diet and to maintain it through the duration of the study.

Exclusion Criteria

Patients are excluded from participation in the study if any of the following criteria apply:

Severe (class IV) heart failure.

Any life-threatening disease expected to result in death within the next 2 years (other than CVD).

Active severe liver disease (evaluated at Visit 1): cirrhosis, active hepatitis, ALT or AST>3×ULN, or biliary obstruction with hyperbilirubinemia (total bilirubin>2× ULN).

Hemoglobin A1c>10.0% (or 86 mmol/mol IFCC units) at screening (Visit 1). If patients fail this criterion (HbA1c>10.0% or 86 mmol/mol IFCC units) at Visit 1, they may have their antidiabetic therapy optimized and be retested at Visit 1.1.

Poorly controlled hypertension: blood pressure≥200 systolic mmHg OR≥100 mmHg diastolic (despite antihypertensive therapy).

Planned coronary intervention (such as stent placement or heart bypass) or any non-cardiac major surgical procedure. Patients can be (re)evaluated for participation in the trial (starting with Visit 1.1) after their recovery from the intervention/surgery.

Known familial lipoprotein lipase deficiency (Fredrickson Type I), apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia (Fredrickson Type III)].

Participation in another clinical trial involving an investigational agent within 90 days prior to screening (Visit 1). Patients cannot participate in any other investigational medication or medical device trial while participating in this study (participation in a registry or observational study without an additional therapeutic intervention is allowed).

Intolerance or hypersensitivity to statin therapy.

Known hypersensitivity to any ingredients of the study product or placebo; known hypersensitivity to fish and or shellfish.

History of acute or chronic pancreatitis.

Malabsorption syndrome and/or chronic diarrhea (Note: patients who have undergone gastric/intestinal bypass sur-

gery are considered to have malabsorption, hence are excluded; patients who have undergone gastric banding are allowed to enter the trial).

Non-study drug related, non-statin, lipid-altering medications, supplements or foods:

Patients are excluded if they used niacin>200 mg/day or fibrates during the screening period (after Visit 1) and/or plan to use during the study; patients who are taking niacin>200 mg/day or fibrates during the last 28 days before Visit 1 need to go through washout of at least 28 days after their last use and have their qualifying lipids measured (TG and LDL-C) after the washout period (Visit 1.1);

Patients are excluded if they take any omega-3 fatty acid medications (prescription medicines containing EPA and/or DHA) during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking omega-3 fatty acid medications during the last 28 days before Visit 1 (except patients in The Netherlands), need to go through a washout period of at least 28 days after their last use and have their qualifying lipids measured (TG and LDL-C) after the washout period (at Visit 1.1);

For patients in The Netherlands only: patients being treated with omega-3 fatty acid medications containing EPA and/or DHA are excluded; no washout is allowed.

Patients are excluded if they use dietary supplements containing omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils) during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking >300 mg/day omega-3 fatty acids (combined amount of EPA and DHA) within 28 days before Visit 1 (except patients in The Netherlands), need to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);

For patients in The Netherlands only: patients being treated with dietary supplements containing omega-3 fatty acids of >300 mg/day EPA and/or DHA are excluded; no washout is allowed.

Patients are excluded if they use bile acid sequestrants during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking bile acid sequestrants within 7 days before Visit 1, need to go through a washout period of at least 7 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);

Other medications (not indicated for lipid alteration):

Treatment with tamoxifen, estrogens, progestins, thyroid hormone therapy, systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are allowed), HIV-protease inhibitors that have not been stable for ≥28 days prior to the qualifying lipid measurements (TG and LDL-C) during screening. To be eligible for participation in the study, patients who are not taking a stable dose of these medications within 28 days before Visit 1, need to go through a stabilization period of at least 28 days since their last dose change and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).

Patients are excluded if they use cyclophosphamide or systemic retinoids during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking these medications within 28 days before Visit 1, need to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).

Known to have AIDS (patients who are HIV positive without AIDS are allowed).

Requirement for peritoneal dialysis or hemodialysis for renal insufficiency or if creatinine clearance (CrCL)<30 mL/min (0.50 mL/sec).

Unexplained creatine kinase concentration>5×ULN or creatine kinase elevation due to known muscle disease (e.g., polymyositis, mitochondrial dysfunction) at Visit 1.

Any condition or therapy which, in the opinion of the investigator, might pose a risk to the patient or make participation in the study not in the patient's best interest.

Drug or alcohol abuse within the past 6 months, and unable/unwilling to abstain from drug abuse and excessive alcohol consumption during the study or drinking 5 units or more for men or 4 units or more for women in any one hour (episodic excessive drinking or binge drinking). Excessive alcohol consumption is on average>2 units of alcohol per day. A unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks.

Mental/psychological impairment or any other reason to expect patient difficulty in complying with the requirements of the study or understanding the goal and potential risks of participating in the study (evaluated at Visit 1).

Study Procedures

Assessment Schedule

Screening Period

Screening Visit (Visit 1)

Patients will come to the Research Site for Visit 1. They will be instructed to fast for at least 10 hours before their visit.

If patients qualify for randomization based on the procedures at Visit 1, they need to be randomized within 60 days after Visit 1. The following procedures will be performed at the screening visit:

Obtain signed informed consent

Assign the patient a patient number

Obtain medical, surgical and family history

Record demographics

Obtain height, weight, and body mass index

Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)

Obtain a 12-lead electrocardiogram

Evaluate inclusion/exclusion criteria

This includes procedures and (fasting) blood samples (for example, hs-CRP, calculated creatinine clearance) as needed to determine the CV risk category (see inclusion criteria)

Obtain fasting blood samples for chemistry and hematology testing

Obtain a fasting blood sample for the lipid profile (TG, TC, HDL-C, LDL-C, non-HDL-C, VLDL-C)

Perform a urine pregnancy test on women of childbearing potential

Record concomitant medication(s)

Instruct patient to fast for at least 10 hours prior to the next visit

Screening Visit (Visit 1.1)

Some patients will skip Visit 1.1: Patients who qualify for study participation after Visit 1 because they meet all inclusion criterion and none of the exclusion criteria, may return to the Research Site for Visit 2 to be randomized and to start the treatment/follow-up period of the study. For these patients, Visit 2 will occur soon after Visit 1.

Patients, who do not qualify at Visit 1, may return to the Research Site for a second qualifying visit (Visit 1.1) at the discretion of the investigator. At Visit 1.1, procedures that caused failure of eligibility at Visit 1 will be repeated. Patients will be eligible for randomization after Visit 1.1 if they meet all inclusion criteria and if they no longer fail the exclusion criteria. If patients are evaluated at Visit 1.1 and qualify for randomization based on the repeated procedures at Visit 1.1, they need to be randomized within 60 days after Visit 1.

For some patients, Visit 1.1 will be mandatory at least 28 days after Visit 1 in order to check eligibility. These are patients who at Visit 1 started treatment with a statin, changed their statin, changed the daily dose of their statin, started to washout prohibited medications or started a stabilization period with certain medications (see inclusion/exclusion criteria for details). Any of these changes at Visit 1 may affect the qualifying lipid levels and therefore, patients will need to have Visit 1.1 to determine whether they qualify based on lipid level requirements (TG and LDL-C) determined at Visit 1. Other procedures that caused failure of eligibility at Visit 1 will also be repeated at Visit 1.1.

The following procedures will be performed at the screening visit:

Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)

Evaluate inclusion/exclusion criteria; only those evaluations will be repeated that deemed the patient not eligible on Visit 1.

Obtain fasting blood samples for chemistry and hematology testing. Only those samples will be obtained that deemed the patient not eligible on Visit 1.

Obtain a fasting blood sample for the lipid profile (TG, TC, HDL-C, LDL-C, non-HDL-C, VLDL-C) if the patient was deemed not eligible on Visit 1. This includes patients who at Visit 1 started treatment with a statin, changed their statin, changed the daily dose of their statin, started to washout prohibited medications or started a stabilization period with certain medications (see inclusion/exclusion criteria for details). These patients will have a fasting blood sample collected at Visit 1.1 for the qualifying lipid values (TG and LDL-C), and the TG and LDL-C inclusion criteria will be evaluated.

Record concomitant medication(s)

Treatment/Follow-Up Period

Every attempt should be made to complete the follow-up visits during the defined window periods.

Randomization visit (Visit 2; Day 0)

Qualified patients will return to the Research Site for Visit 2.

The following procedures will be performed at Visit 2:

Perform physical examination

Obtain weight

Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)

Measure waist circumference (one of the factors to diagnose metabolic syndrome)

Obtain a 12-lead electrocardiogram

Evaluate inclusion/exclusion criteria

Obtain fasting blood samples for:

Chemistry and hematology testing

Lipid profile (baseline)

Biomarker assays (baseline)

Genetic testing (optional blood sample)

Archiving (in countries and at sites approved by IRB/IEC and dependent on country regulations)

Perform a urine pregnancy test on women of childbearing potential (must be negative for randomization)

Dispense study drug and record randomization number

Instruct patient on how to take study drug

Administer study drug—Note: Study drug should be taken orally with food following the collection of all fasting blood samples

Assess for and record adverse events

Record concomitant medication(s)

Instruct patient:

To bring all study supplies with them to the next visit

Not to take study drug on the morning of their next visit

To fast for ≥10 hours prior to the next visit

Visit 3 (Day 120; ~4 Months)

Patients will return to the Research Site for Visit 3 on Day 120±10 days.

The following procedures will be performed:

Perform physical examination

Obtain weight

Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)

Obtain fasting blood samples for:

Chemistry and hematology testing

Lipid profile

Review study drug compliance by unused capsule count; discuss with and counsel patients about compliance if needed

Administer study drug—Note: Study drug should be taken orally with food following the collection of all fasting blood samples

Assess and record efficacy events

Assess for and record adverse events

Record concomitant medication(s)

Instruct patient:

To bring all study supplies with them to the next visit

Not to take study drug on the morning of their next visit

To fast for ≥10 hours prior to the next visit

Visits 4, 5, 6 and 7

At Visit 4: Day 360±10; Visit 5: Day 720±10; Visit 6: Day 1080±10; and Visit 7: Day 1440±10, the following procedures will be performed:

Perform physical examination

Obtain weight

Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)

Measure waist circumference (collected at Visit 5 only)

Obtain a 12-lead electrocardiogram

Obtain fasting blood samples for:

Chemistry and hematology testing

Lipid profile

Biomarker assays (collected at Visit 5 only)

Archiving (in countries and at sites approved by IRB/IEC and dependent on country regulations)

Review study drug compliance by unused capsule count; discuss with and counsel patients about compliance if needed

Administer study drug—Note: Study drug should be taken orally with food following the collection of all fasting blood samples

Assess and record efficacy events

Assess for and record adverse events

Record concomitant medication(s)

Instruct patient:

To bring all study supplies with them to the next visit

Not to take study drug on the morning of their next visit

To fast for ≥10 hours prior to the next visit

Additional Visits

The end date of the study is expected for Day 1800 but the actual end date will be dependent on the determination of the study end date by the DMC. The study end date is determined to be when approximately 1612 primary efficacy events have occurred. If the actual study end date is later than the expected end date, additional visits will be planned between Visit 7 and the Last Visit with a maximum of 360±10 days between visits. If the actual study end date is sooner than the expected end date, fewer visits will occur, and the last visit (See Section 6.1.2.5) will occur sooner.

On additional visits the same procedures will be performed as listed in Section 6.1.2.3. Irrespective of the number of additional visits, after the DMC has established the end of the study date, there will be a last visit with procedures as listed in Section 6.1.2.5.

Last Visit—End of Study

All patients will complete the study at the same time (within a 30-day window after the study end date), irrespective of the date that they were randomized. The end date of the study is planned for Day 1800 but the actual end date will be dependent on the determination of the study end date when approximately 1612 primary efficacy events have occurred (event-driven trial). For each patient, the last visit may occur within 30 day after the actual study end date. However, for the efficacy endpoints based on CV events, only events occurring up to and including the scheduled actual study end date will be included in the efficacy analyses.

A final follow-up visit is required for all patients. In the rare cases that a final follow-up visit cannot occur within the 30-day timeframe following the study end date, any attempt to contact the patient must be recorded on a special contact form, until/unless appropriate information is obtained.

At the Last Visit, the following procedures will be performed:

Perform physical examination

Obtain weight

Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)

Measure waist circumference

Obtain a 12-lead electrocardiogram

Obtain fasting blood samples for:

Chemistry and hematology testing

Lipid profile

Biomarker assays

Archiving (in countries and at sites approved by IRB/IEC and dependent on country regulations)

Determine study drug compliance by unused capsule count

Assess and record efficacy events

Assess for and record adverse events

Record concomitant medication(s)

Telephone Follow-up Contact

Site personnel will contact each patient by telephone on the following study days:

Day 60±3 days

Day 180±5 days

Day 270±5 days

Day 450±5 days

Day 540±5 days

Day 630±5 days

Day 810±5 days

Day 900±5 days

Day 990±5 days

Day 1170±5 days

Day 1260±5 days

Day 1350±5 days

Day 1530±5 days

Day 1620±5 days

Day 1710±5 days

If the treatment/follow-up period of the study is extended beyond the expected end date (Day 1800), additional follow-up phone calls will be made every 3 months in-between additional visits±5 days. If the treatment/follow period of the study is shorter than the expected end date, less follow-up phone calls will be needed.

Every attempt will be made to talk to each patient within this time frame.

The following information will be collected from the patient:

Possible efficacy endpoints related to CV events. Patients will be asked to return to the Research Site to assess for any endpoints or events identified.

Adverse events

Concomitant medications

Current address and contact information (update if changed or will be changing)

Patients will be reminded about the following items:

To take the study medication according to the dosing schedule assigned, with food

When to return to the Research Center for the next visit

To bring the unused study medication to the next visit

To not take study drug on the morning of their next visit

To fast for at least 10 hours prior to the next visit

Laboratory Procedures

Clinical Laboratory Procedures

All clinical laboratory determinations for screening and safety will be performed by a certified clinical laboratory under the supervision of the Sponsor or its designee.

Whenever possible and appropriate, samples for the clinical laboratory procedures will be collected after fasting for at least 10 hours. For the purposes of this study, fasting is defined as nothing by mouth except water (and any essential medications).

The investigator must review and sign all laboratory test reports. At screening, patients who have laboratory values that are outside the exclusionary limits specified in the exclusion criteria may not be enrolled in the study (patients can be considered for the study if values are classified as not clinically significant by the investigator). After randomization, the investigator will be notified if laboratory values are outside of their normal range. In this case, the investigator will be required to conduct clinically appropriate follow-up procedures.

Safety Laboratory Tests

The safety laboratory tests include:

Hematology with complete blood count (CBC), including RBC, hemoglobin (Hgb), hematocrit (Hct), white cell blood count (WBC), white cell differential, and platelet count

Biochemistry panel including total protein, albumin, alkaline phosphatase, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), total bilirubin, glucose, calcium, electrolytes (sodium, potassium, chloride), blood urea nitrogen (BUN), serum creatinine, uric acid, creatine kinase, and HbA1c.

Fasting Lipid Profile

The fasting lipid panel includes: TG, TC, LDL-C, HDL-C, non-HDL-C, and VLDL-C.

At all visits, LDL-C will be calculated using the Friedewald equation. At Visit 1 and Visit 1.1 Direct LDL-C will be used if at the same visit TG>400 mg/dL (4.52 mmol/L). These LDL-C values will be used for the evaluation of the LDL-C inclusion criterion (LDL-C qualifying measure-

ments for randomization) and for the assessment of changes in the statin therapy when LDL-C is not at goal. At all remaining visits (except Visit 2 and Visit 4) LDL-C will be measured by Direct LDL Cholesterol or by Preparative Ultracentrifugation if at the same visit TG>400 mg/dL (4.52 mmol/L). In addition, irrespective of the TG levels, at Visit 2 (0 Months of Follow-up, baseline) and at Visit 4 (12 Months of Follow-up), LDL-C will be measured by Preparative Ultracentrifugation. These Preparative Ultracentrifugation LDL-C measurements will be used in the statistical analysis including the calculation of the percent change from baseline (1 year versus baseline).

Genetic Testing

A fasting blood sample will be stored for future genetic testing at the discretion of the sponsor. The specifics of this test will be determined at a later date. This sample is optional as local regulations may prohibit genetic samples to be collected or shipped outside the country, or patients may not consent.

Research on genetic testing will look for links between genes and certain diseases, including their treatment(s) such as medicines and medical care. The blood samples will be collected in the study center with the regular protocol-required labs. Each patient tube with sample for genetic testing will be labeled with patient number only. The site will maintain a Subject Code Identification List for cross-reference. The patient number does not contain any identifiable information (i.e. Patient initials, date of birth, etc). Un-analyzed samples will be stored frozen by the sponsor for a period of up to 2 years following the end of the study, at which time they will be destroyed. If samples are tested, results will not be reported to the patient, parents, relatives, or attending physician and will not be recorded in the patient's medical records. There will be no follow-up contact with the sites or patients regarding this sample. The subject can withdraw their consent for genetic testing at any time up to analysis, even after the sample has been obtained. The subject can notify the site in writing that they withdraw their consent for the genetic testing portion of the study, and it will be documented by the site in the subject chart, as well as captured in the CRF. The lab will be notified to pull the sample and destroy it.

Biomarkers Assays

The biomarker assays include: hs-CRP, Apo B and hsTnT.

Additional laboratory tests

Additional laboratory tests include:

A urine pregnancy test will be administered to women of childbearing potential at certain visits as listed in schedule of procedures (Table 1). The urine pregnancy tests will be performed at the Research Site utilizing marketed test kits, or at a certified clinical laboratory.

A fasting blood sample (12 mL) for archiving. This sample will be collected only at sites in countries where allowed by local regulations and at sites for which approved by the IRB or IEC. The plasma from the archiving sample will be stored frozen in 2 separate equal aliquots, and will be used at the Sponsor's discretion to perform repeat analyses described in the protocol or to perform other tests related to cardiovascular health.

Blinding of Laboratory Results

All efficacy laboratory results during the double-blind period of the trial will be blinded (values not provided) to patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and personnel at the organization(s) and vendors managing and/or supporting the study, with the exception of the laboratory personnel conducting the assays. To ensure patient safety, hsTnT values will be reported to the site.

Flagging of Critical Lab Values

Critical lab values are values that may warrant medical intervention to avoid possible harm to a patient. Critical lab values will be defined in the Laboratory Manual for the study, and the Research Site will be notified of the occurrence of a critical lab value (critical high or critical low) by a special annotation (flag) in the laboratory reports provided to the Research Sites. Although laboratory values that are part of the efficacy endpoints during the double-blind period of the study will not be provided to the Research Site (see Section 6.3.1.6), the sites will be notified when the TG value of a patient sample is >1000 mg/dL (11.29 mmol/L) (critical high TG value) or if the LDL-C values of a patient sample is >130 mg/dL (3.37 mmol/L) (critical high LDL-C value). These critical high values will need to be confirmed by a repeat measurement (new fasting blood sample) within 7 days. TG value of >2000 mg/dL (22.58 mmol/L) will also be flagged, so that appropriate medical action can be taken by the investigator as soon as possible.

If TG values are confirmed critically high, patients may be discontinued from study drug with the option to remain on study. The investigator should use the best clinical judgment for each patient which could include the use of approved TG-lowering medications after patients have been discontinued from study drug.

If LDL-C values are confirmed critically high, the investigator may need to take appropriate medical action which could include: reinforce/intensify therapeutic lifestyle changes (including diet and physical activity), increase the dose of the present statin therapy, add ezetimibe, or prescribe a more potent statin to lower LDL-C. The investigator should use the best clinical judgment for each patient.

Medical Procedures

Medical, Surgical and Family History

Medical history, including family history and details regarding all illnesses and allergies, date(s) of onset, status of current condition, and smoking and alcohol use will be collected on all patients.

Demographics

Demographic information including day, month, and year of birth, race, and gender will be collected for all patients.

Vital Signs

Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. Blood pressure will be measured using a standardized process:

Patient should sit for ≥5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level.

Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery.

Blood pressure should be recorded to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device. A blood pressure reading should be repeated 1 to 2 minutes later, and the second reading should also be recorded to the nearest 2 mmHg mark.

Physical Examination

A physical examination must include source documentation of general appearance, skin, and specific head and neck, heart, lung, abdomen, extremities, and neuromuscular assessments.

Height, Weight and Body Mass Index

Height and weight will be measured. Measurement of weight should be performed with the patient dressed in indoor clothing, with shoes removed, and bladder empty.

Waist Circumference

Waist circumference will be measured with a tape measure, as follows: Start at the top of the hip bone then bring the tape measure all the way around—level with the navel. Make sure the tape measure is snug, but without compressing the skin, and that it is parallel with the floor.

Patients should not hold their breath while measuring waist circumference.

Electrocardiogram (ECG)

ECGs (standard 12-lead) will be obtained annually. Site personnel should make every attempt to perform a patient's ECG using the same equipment at each visit. ECGs will be reviewed by the site for the detection of silent MI. Silent MIs will be sent for event adjudication.

Treatment and Restrictions

Treatment

Treatment Regimen, Dosage, and Duration

Eligible study patients will be randomly assigned on Day 0 to one of the 2 treatment groups. Patients in each group will receive either 4 g/day AMR101 or placebo for up to 4.75 years (4 years planned median treatment duration) according to Table 2.

The daily dose of study drug is 4 capsules per day taken as two capsules take on two occasions per day (2 capsules given twice daily).

TABLE 2

Dosing Schedule during the Treatment Period

Treatment Group	Daily Dose	Number of Capsules per Day
1	4 g	4 capsules of 1000 mg AMR101
2	Placebo	4 capsules of matching placebo

Patients will be instructed to take study drug with food (i.e., with or at the end of their morning and evening meals). On days that patients are scheduled for study visits, the daily dose of study drug will be administered by site personnel with food provided by the site following collection of all fasting blood samples. For the purposes of this study, fasting is defined as nothing by mouth except water (and any essential medications) for at least 10 hours.

Treatment Assignment

Identification Number

A unique patient identification number (patient number) will be established for each patient at each site. The patient number will be used to identify the patient throughout the study and will be entered on all documentation. If a patient is not eligible to receive treatment, or if a patient discontinues from the study, the patient number cannot be reassigned to another patient. The patient number will be used to assign patients to one of the 2 treatment groups according to the randomization schedule.

Drug Randomization

Only qualified patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized and will receive study medication starting at Visit 2 (Day 0). Eligible patients will be randomly assigned to one of the 2 treatment groups. Randomization will be stratified by CV risk category, use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries) (See Section 3.10). Approximately 70% of randomized patients will be in the CV Risk Category 1, including patients with established CVD, and approximately 30% of randomized patients will be in the CV Risk Category 2, including patients with diabetes and at least one additional risk factor but no established CVD. Enrollment with patients of a CV risk category will be stopped when the planned number of patients in that risk category is reached.

Emergency Unblinding

In an emergency, when knowledge of the patient's treatment assignment is essential for the clinical management or welfare of the patient, the investigator may request the patient's treatment assignment for unblinding. Prior to unblinding the patient's individual treatment assignment, the investigator should assess the relationship of an adverse event to the administration of the study drug (Yes or No). If the blind is broken for any reason, the investigator must record the date and reason for breaking the blind on the appropriate Case Report Form (CRF) and source documents.

Compliance Control

It is recommended that, unless clear contraindications arise, patients be strongly encouraged to adhere to their treatment regimen with the study drug for the duration of the trial. Any interruptions of therapy should, if possible, be brief (e.g., <4 weeks) and only for clinically indicated reasons, such as adverse events. Discontinuations will be discouraged as much as possible. Any discontinuations should be based on compelling clinical reasons.

For every patient, an assessment of compliance to the study drug treatment regimen must be obtained at each scheduled visit. Study medication will be dispensed in amounts exceeding the amount required for the study. Patients will be instructed to return all unused study medication at the next visit. Compliance to the study drug regimen will be evaluated at each visit by counting unused capsules. Discrepancies will be evaluated and discussed with each patient to assess compliance. If compliance is unsatisfactory, the patient will be counseled about the importance of compliance to the dosing regimen. At the end of the study, the final study medication compliance will be determined by unused capsule count.

Study Restrictions

Concomitant Medications During Treatment/Follow-Up Period

Any medications administered during the study period must be documented on the Concomitant Medication CRF. Patients must not have taken any investigational agent within 90 days prior to screening. Patients cannot participate in any other investigational medication trial while participating in this study.

The following non-study drug related, non-statin, lipid-altering medications and supplements, and foods are prohibited during the study (from Visit 1 until after the Last Visit-End of Study), except for compelling medical reasons in ODIS patients:

niacin>200 mg/day;

fibrates;

prescription omega-3 fatty acid medications;

dietary supplements containing omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils);

bile acid sequestrants;

cyclophosphamide;

systemic retinoids

If any of these products would be used during the treatment/follow-up period of the study, it should be for compelling medical reasons in ODIS patients, and it should be documented in the Concomitant Medication CRF. If the

ODIS patient agrees to restart study medication, the use of excluded medication must be discontinued.

Foods enriched with omega-3 fatty acids are strongly discouraged after Visit 1 for the duration of the study (does not apply to The Netherlands or Canada only. Therefore, all centers in The Netherlands and Canada must ignore this request).

The following products are allowed: statins, ezetimibe, and herbal products & dietary supplements not containing omega-3 fatty acids.

Statins:

The same statin at the same dose should be continued until the end of the study, unless deemed medically necessary to change because of an adverse event or lack of efficacy (LOE). It is preferred that if LOE is the determining factor that ezetimibe be added to the present dose.

Switching between a brand name statin and the generic version of the same statin is allowed at any time during the study.

Statins may be administered with or without ezetimibe.

Based on the FDA recommendation, simvastatin 80 mg be used only in patients who have been taking this dose for 12 months or more and have not experienced any muscle toxicity. (See reference: FDA Drug Safety Communication: Ongoing safety review of high-dose Zocor (simvastatin) and increased risk of muscle injury. (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm204882.htm)

Changing of the type of statin or the statin dose during the treatment/follow-up period of the study should only be done for compelling medical reasons and must be documented in the CRF.

LDL-C Rescue:

If the level of LDL-C exceeds 130 mg/dL (3.37 mmol/L) during the study (initial measurement and confirmed by a second determination at least 1 week later), the investigator may either increase the dose of the present statin therapy or may add ezetimibe to lower LDL-C. The investigator should use the best clinical judgment for each patient.

No data are available with regard to potential interactions between ethyl-EPA and oral contraceptives. There are no reports suggesting that omega-3 fatty acids, including ethyl-EPA, would decrease the efficacy of oral contraceptives.

Patient Restrictions

Beginning at the screening visit, all patients should be instructed to refrain from excessive alcohol consumption, to follow a physician recommended diet and to maintain it through the duration of the study. Excessive alcohol consumption is on average 2 units of alcohol per day or drinking 5 units or more for men or 4 units or more for women in any one hour (episodic excessive drinking or binge drinking). A unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks.

Investigational Product

Clinical Trial Material

The following will be supplied by the Sponsor:

AMR101 1000 mg capsules

Placebo capsules

The Sponsor will supply sufficient quantities of AMR101 1000 mg capsules and placebo capsules to allow for completion of the study. The lot numbers of the drugs supplied will be recorded in the final study report.

Records will be maintained indicating the receipt and dispensation of all drug supplies. At the conclusion of the study, any unused study drug will be destroyed.

Pharmaceutical Formulations

AMR101 1000 mg and placebo capsules (paraffin) are provided in liquid-filled, oblong, gelatin capsules. Each capsule is filled with a clear liquid (colorless to pale yellow in color). The capsules are approximately 25.5 mm in length with a diameter of approximately 9.5 mm.

Labeling and Packaging

Study medication will be packaged in high-density polyethylene bottles. Labeling and packaging will be performed according to GMP guidelines and all applicable country-specific requirements. The bottles will be numbered for each patient based on the randomization schedule. The patient randomization number assigned by IWR or a designee of the Sponsor for the study (if no IWR system is used), will correspond to the number on the bottles. The bottle number for each patient will be recorded in the Electronic Data Capture (EDC) system for the study.

Dispensing Procedures and Storage Conditions

Dispensing Procedures

At Visit 2 (Day 0), patients will be assigned study drug according to their treatment group determined by the randomization schedule. Once assigned to a treatment group, patients will receive study drug supplies. At each visit, patients will bring unused drug supplies dispensed to them earlier. From the drug supplies assigned to each patient, site personnel will administer drug while the patients are at the Research Site.

The investigator or designee must contact the IWR system or a designee of the Sponsor for the study (if no IWR system is used) when any unscheduled replacements of study medication are needed.

During the last visit during the treatment period, patients will bring the unused drug supplies for site personnel to calculate the final study medication compliance by unused capsule count.

Storage Conditions

At the Research Sites, study drugs must be stored at room temperature, 68° F. to 77° F. (20° C. to 25° C.). Do not allow storage temperature to go below 59° F. (15° C.) or above 86° F. (30° C.). Store in the original package.

Study drugs must be stored in a pharmacy or locked and secure storage facility, accessible only to those individuals authorized by the investigator to dispense the drug. The investigator or designee will keep accurate dispensing records. At the conclusion of the study, study site personnel will account for all used and unused study drug. Any unused study drug will be destroyed. The investigator agrees not to distribute study drug to any patient, except those patients participating in the study.

Efficacy Assessments

Specification of Variables and Procedures

The primary endpoint and the majority of the secondary and tertiary endpoints are based on clinical events related to CVD and mortality. All events occurring between randomization and the study end date (inclusive) must be recorded. Only adjudicated events will be included in the final analyses. Further details on the assessment of clinical events and their definitions will be found in the CEC charter.

Efficacy Endpoints

Primary Efficacy Endpoint

Time from randomization to the first occurrence of the composite of the following clinical events:

CV death,

Nonfatal MI (including silent MI; ECGs will be performed annually for the detection of silent MIs),

Nonfatal stroke,

Coronary revascularization

Hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing.

The first occurrence of any of these major adverse vascular events during the follow-up period of the study will be included in the incidence.

Secondary Efficacy Endpoints

The key secondary efficacy endpoint is:

The composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or peripheral CVD requiring intervention, angioplasty, bypass surgery, or aneurysm repair.

Other secondary efficacy endpoints are as follows (to be tested in said order):

The composite of total mortality, nonfatal MI, or nonfatal stroke;

The composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, peripheral CVD requiring intervention, or cardiac arrhythmia requiring hospitalization;

The composite of death from CV causes, nonfatal MI, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;

The composite of death from CV causes or nonfatal MI;

Total mortality;

Fatal and nonfatal MI (including silent MI);

Coronary Revascularization;

Hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing;

Fatal and nonfatal stroke.

For the secondary endpoints that count a single event, the first occurrence of this type of event will be counted in each patient. For secondary endpoints that are composites of two or more types of events, the first occurrence of any of the event types included in the composite will be counted in each patient.

Tertiary Efficacy Endpoints:

The second, third, fourth, and fifth major CV event of the primary composite endpoint. The type of (nonfatal) events may occur in any order.

Primary endpoint in subset of patients with diabetes mellitus;

Primary endpoint in subset of patients with metabolic syndrome;

New CHF, new CHF leading to hospitalization, transient ischemic attack, amputation for CVD and carotid revascularization;

Elective coronary revascularization and emergent coronary revascularization;

New onset diabetes;

Fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hs-CRP, and hsTnT: effect of baseline and on-treatment change of biomarkers on primary and key secondary endpoints;

CV mortality;

Cardiac Arrhythmias requiring hospitalization;

Cardiac Arrest;

To explore the effect of AMR101 on weight and waist circumference.

For the tertiary endpoints that count a single event, the first occurrence of this type of event will be counted in each patient. For tertiary endpoints that are composites of two or more types of events, the first occurrence of any of the event types included in the composite will be counted in each patient (except when stated otherwise, for the second, third, fourth, and fifth major CV event).

Safety Assessments

Specification of Variables and Procedures

Safety assessments will include adverse events, clinical laboratory measurements (chemistry, hematology), 12-lead ECGs, vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature), and physical examinations as per Study Procedures/Table 1.

A complete medical, surgical and family history will be completed at Visit 1.

All laboratory test results must be evaluated by the investigator as to their clinical significance. Any observations at physical examinations or laboratory values considered by the investigator to be clinically significant should be considered an adverse event.

Adverse Events

An adverse event is defined as any untoward medical occurrence, which does not necessarily have a causal relationship with the medication under investigation. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medication product, whether or not related to the investigational medication product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate CRF. Each adverse event is to be evaluated for duration, intensity, and causal relationship with the study medication or other factors.

Adverse events, which include clinical laboratory test variables, will be monitored from the time of informed consent until study participation is complete. Patients should be instructed to report any adverse event that they experience to the investigator. Beginning with Visit 2, investigators should assess for adverse events at each visit and record the event on the appropriate adverse event CRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the CRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate adverse event on the CRF.

Any medical condition that is present when a patient is screened or present at baseline that does not deteriorate should not be reported as an adverse event. However, medical conditions or signs or symptoms present at baseline and that change in severity or seriousness at any time during the study should be reported as an adverse event.

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen will be reported as adverse events or SAEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

The investigator will rate the severity (intensity) of each adverse event as mild, moderate, or severe, and will also categorize each adverse event as to its potential relationship to study drug using the categories of Yes or No.

Severity:

Mild—An event that is usually transient in nature and generally not interfering with normal activities.

Moderate—An event that is sufficiently discomforting to interfere with normal activities.

Severe—An event that is incapacitating with inability to work or do usual activity or inability to work or perform normal daily activity.

Causality Assessment:

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, no relation)—The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Yes—The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The following factors should also be considered:

The temporal sequence from study medication administration

The event should occur after the study medication is given. The length of time from study medication exposure to event should be evaluated in the clinical context of the event.

Underlying, concomitant, intercurrent diseases

Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

Concomitant medication

The other medications the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.

Known response pattern for this class of study medication

Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

Exposure to physical and/or mental stresses

The exposure to stress might induce adverse changes in the patient and provide a logical and better explanation for the event.

The pharmacology and pharmacokinetics of the study medication

The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study medication should be considered.

Unexpected Adverse Events—An unexpected adverse event is an adverse event either not previously reported or where the nature, seriousness, severity, or outcome is not consistent with the current Investigator's Brochure.

Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that meets any of the following criteria:

Results in death

Is life-threatening—Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires hospitalization or prolongation of existing hospitalization—Note: In general, hospitalization for treatment of a pre-existing condition(s) that did not worsen from baseline is not considered adverse events and should not be reported as SAEs.

Results in disability/incapacity

Is a congenital anomaly/birth defect;

Is an important medical event—Note: Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

By design of this study SAEs that are endpoint events will only be recorded for the endpoint determination and not captured as SAEs. The intention is that the endpoint events are not reported to IRBs as SAEs, unless the IRB requires that these are reported. Investigators should specifically inform their institution/IRB of this plan and confirm whether or not they want the endpoint events reported. By agreement with the US FDA, these endpoints will also not be reported to the US FDA as SAEs; rather they will be reported as endpoint events. Following adjudication if the event is determined to not meet the criteria for an event, the event will be evaluated as an SAE beginning with that day as Day 0.

Serious Adverse Event Reporting—Procedure for Investigators

Initial Reports

All SAEs occurring from the time of informed consent until 28 days following the last administration of study medication must be reported to the Sponsor or designee within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). SAEs that the investigator considers related to study medication occurring after the 28-day follow-up period will also be reported to the Sponsor or designee.

The investigator is required to submit SAE reports to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) in accordance with local requirements. All investigators involved in studies using the same investigational medicinal product (IMP) will receive any Suspected Unexpected Serious Adverse Reaction (SUSAR) reports for onward submission to their local IRB as required. All reports sent to investigators will be blinded.

In addition, regulatory agencies will be notified of SAEs per the requirements of the specific regulatory jurisdiction regulations and laws.

Follow-Up Reports

The investigator must continue to follow the patient until the SAE has subsided, or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies. Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., laboratory test reports, patient discharge summary, or autopsy reports) to the Sponsor or designee via fax or email.

Reporting by the Sponsor

IRBs and IECs will be informed of SUSARs according to local requirements. Cases will be unblinded for reporting purposes as required.

Exposure In Utero During Clinical Trials

If a patient becomes pregnant during the study, the investigator should report the pregnancy to the Sponsor or designee within 24 hours of being notified. The Sponsor or designee will then forward the Exposure In Utero form to the investigator for completion.

The patient should be followed by the investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the Sponsor or designee. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

Treatment Discontinuation/Patient Withdrawal

Patients may withdraw from the study at any time and for any reason. Study drug administration may also be discontinued at any time, at the discretion of the investigator. In any case, follow-up for efficacy and safety should be continued.

Reasons for Early Study Drug Discontinuation

Study drug discontinuation should be avoided as much as possible, but may be done for any of the following reasons:

Patient withdraws consent or requests early discontinuation from the study for any reason. Patients should be encouraged to continue to participate in the study for the entire duration of the study even if they choose not to take study medication any longer.

Occurrence of a clinical or laboratory adverse event, either serious or non-serious, at the discretion of the investigator. The Sponsor or designee should be notified if a patient is discontinued because of an adverse event or laboratory abnormality. It is recommended that, unless clear contraindications arise, patients be strongly encouraged to adhere to their treatment regimen with the study drug for the duration of the trial. Any interruptions of therapy should, if possible, be brief (e.g., <4 weeks) and only for clinically indicated reasons, such as adverse events. The following should be considered reason for discontinuation:

ALT>3×ULN and bilirubin>1.5×ULN

ALT>5×ULN

ALT>3×ULN and appearance or worsening of hepatitis

ALT>3×ULN persisting for >4 weeks

ALT>3×ULN and cannot be monitored weekly for 4 weeks

Any medical condition or personal circumstance that, in the opinion of the investigator, exposes the patient to risk by continuing in the study or precludes adherence to the protocol.

Sponsor discontinues the study.

A TG value that is flagged as critically high, i.e., >1000 mg/dL (11.29 mmol/L), and confirmed as critically high by a repeat measurement (new fasting blood sample) within 7 days. In this case, a patient may be discontinued from study drug (with the option to remain ODIS) and other lipid-altering medications may be (re)initiated. If the TG value is flagged as >2000 mg/dL (22.58 mmol/L) then appropriate medical action can be taken by the investigator as soon as possible.

Occurrence of an outcome event according to the judgment of the investigator is not considered a valid reason for study drug discontinuation.

Patients whose treatment with study medication is discontinued early, and have not withdrawn consent, will stay in study and will be monitored until the end of the study. Patients that continue in the study after indefinite cessation of therapy will be characterized as Off Drug In Study (ODIS). ODIS patients should be asked to return to the study site for an interim visit once the patient has been off study drug for >30 days. Procedures at this visit are consistent with those at Visit 5. If not contraindicated, patients will also have the option to restart study medication at any point once characterized as ODIS.

The reason for study drug discontinuation or interruption will be recorded on the CRF.

Follow-Up after Early Study Drug Discontinuation/Lost to Follow-Up

Patients who prematurely discontinue study drug are not to be replaced.

All randomized patients must be followed up according to the study flowchart until the study end date or death, regardless of whether they discontinue study drug prematurely or not. Any event occurring after early study drug discontinuation will be recorded up through the study end date.

In order to follow the medical status of the patients, especially when they discontinued the study, investigators are encouraged to obtain information from the patient's primary care practitioner (physician or any other medical care provider). Investigators are also requested to try as much as possible to re-contact those patients at the end of the trial to obtain at least their vital status as well as their status with respect to the primary endpoint, and thus avoid lost to follow-up for the efficacy assessment.

If patients are lost to follow-up, the CRF must be completed up to the last visit or contact.

Statistics

Analysis Populations

Randomized Population

The randomized population will include all patients who sign the informed consent form and are assigned a randomization number at Visit 2 (Day 0).

Intent-to-Treat Population

The Intent-to-Treat (ITT) population will consist of all randomized patients who take at least one dose of study drug. The ITT population is the primary analysis population. All efficacy analyses will be performed on the ITT population.

Per-Protocol Population

The per-protocol (PP) population will include all ITT patients without any major protocol deviations, and who had ≥80% compliance with study drug while on treatment (up to discontinuation for patients whose treatment is terminated early). The per-protocol efficacy analysis for CV events will be restricted to each patient's time on study drug plus 30 days thereafter.

Safety Population

All safety analyses will be conducted based on the safety population, which is defined as all randomized patients who receive at least one dose of study drug. This is the same as the ITT population.

Statistical Methods

Safety and efficacy variables will be analyzed using appropriate statistical methods to be described in detail in a separate Statistical Analysis Plan (SAP). The SAP will be finalized before study unblinding.

Patient Disposition and Demographic/Baseline Characteristics

The numbers of patients screened, the number of patients randomized per treatment group (randomized population), and the number of patients in the ITT and PP populations by treatment group will be listed.

For randomized patients who discontinued treatment with study drug, the primary reason for discontinuation will be listed and summarized by treatment group.

Summary statistics (mean, standard deviation, median, minimum and maximum) will be provided by treatment

group for demographic characteristics (e.g., age, sex, race, and ethnicity) and baseline characteristics (e.g., body weight, height, and body mass index) in the ITT and PP populations.

Demographic data and baseline characteristics will be compared among treatment groups for the ITT and PP population. Differences in demographic and baseline characteristics will be tested using a chi-square test (for categorical variables) or a 1-way analysis of variance model with treatment as a factor (for continuous variables). The p-values will be used as descriptive statistics, primarily as an assessment of the adequacy of randomization.

Study Medication Exposure and Compliance

The final compliance to study drug will be calculated as the percent of doses taken relative to doses scheduled to be taken. Overall percent compliance will be calculated per patient in the ITT and PP populations and summarized by treatment group using summary statistics (n, mean, standard deviation, median, minimum, and maximum).

Concomitant Therapies

Concomitant medication/therapy verbatim terms will be coded using the latest version of the World Health Organization Drug Dictionary. The numbers and percentages of patients in each treatment group taking concomitant medications will be summarized by anatomic and therapeutic chemical classification and preferred term.

Analysis of Efficacy

For efficacy endpoints including CV events, only adjudicated events will be included in the final statistical analyses.

Summary Statistics

Summary statistics (n, mean, standard deviation, median, minimum, and maximum) for the baseline and post-baseline measurements, the percent changes, or changes from baseline will be presented by treatment group and by visit for all efficacy variables to be analyzed. The summary statistics will include changes in body weight and body mass index from baseline by treatment group and by visit.

Primary Endpoint

The primary efficacy endpoint is the time from randomization to the first occurrence of any component of the composite of the following clinical events:

CV death,

Nonfatal MI (including silent MI),

Nonfatal stroke,

Coronary revascularization,

Hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing.

The analysis of the primary efficacy endpoint will be performed using the log-rank test comparing the 2 treatment groups (AMR101 and placebo) and including the stratification factor "CV risk category", use of ezetimibe and geographical region (Westernized, Eastern European, and Asia Pacific countries) (each as recorded in the IWR at the time of enrollment) as covariates. Treatment difference will be tested at alpha level of 0.0476 accounting for one interim efficacy analysis. The hazard ratio for treatment group (AMR101 vs. placebo) from a Cox proportional hazard model that includes the stratification factor will also be reported, along with the associated 95% confidence interval. Kaplan-Meier estimates from randomization to the time to the primary efficacy endpoint will be plotted.

The size and direction of the treatment effects of the individual components of the composite endpoint and their relative contribution to the composite endpoint will be determined as well.

Secondary Endpoints

The statistical analyses of the secondary endpoints will be analyzed by the same log-rank test specified above for the primary efficacy endpoint. Treatment differences will be tested at alpha level of 0.05 using a sequential procedure for controlling type 1 error starting with the key secondary variable. The remaining secondary variables will be tested in the order specified in Section 9.2.2. Estimates of the hazard ratios from the Cox proportional hazard model and the associated 95% confidence intervals will also be provided. Kaplan-Meier estimates from randomization the time to the secondary efficacy endpoints will be plotted.

Tertiary Endpoints

For event rates, the statistical analyses of the tertiary endpoints will be similar to the analysis of the secondary efficacy endpoints. All tertiary analyses will be conducted for the ITT population. No adjustments for multiple testing will be made.

For measurements of lipids, lipoproteins and inflammatory markers the change from baseline will be analyzed in the units of each marker, and the percent change from baseline. Since these biomarkers are typically not normally distributed, the Wilcoxon rank-sum test will be used for treatment comparisons of the percent change from baseline, and medians and quartiles will be provided for each treatment group. The medians of the differences between the treatment groups and 95% confidence intervals will be estimated with the Hodges-Lehmann method.

New onset diabetes is defined as Type 2 diabetes newly diagnosed during the treatment/follow-up period (i.e. patients with no history of diabetes at randomization).

For purposes of this study, a diagnosis of diabetes is made based on the observation of:

1. $HbA_{1c} \geq 6.5\%$. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay. In the absence of unequivocal hyperglycemia, $HbA_{1c} > 6.5\%$ should be confirmed by repeat testing.

OR

2. Fasting plasma glucose (FPG)≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hr. In the absence of unequivocal hyperglycemia, FPG≥126 mg/dL (7.0 mmol/L) should be confirmed by repeat testing.

OR

3. 2-hr plasma glucose≥200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. In the absence of unequivocal hyperglycemia, 2-hr plasma glucose≥200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT) should be confirmed by repeat testing.

OR

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose≥200 mg/dL (11.1 mmol/L).

Exploratory Subgroup Analyses

Subgroup analyses of the primary and key secondary endpoints (as defined in the Statistical Analysis Plan) will be performed. All subgroup analyses will be conducted for the ITT population. No adjustments for multiple testing will be made.

Log-rank tests, treatment effects and the associated 95% confidence intervals for the primary and key secondary efficacy endpoints within each subgroup will be provided using the Cox proportional hazard model with treatment

(AMR101 or placebo), and stratification as a factor (with the exception of the subgroup analyses of those subgroup variables related to the stratification factors, i.e., CV risk category that will not have stratification as a factor).

Subgroups including, but not limited to the following, will be explored. A complete list will be prospectively defined in the Statistical Analysis Plan.

Demographics:

Gender,

age (<65 yr and ≥65 yr),

race (white and nonwhite, or any other subset with at least 10% of the total number of patients),

geography (western vs. non-western)

Disease Parameters:

CV risk category,

the presence/absence of diabetes at baseline,

renal impairment

Treatment Parameters:

by statin intensity (statin type and regimen),

relevant concomitant medications,

Baseline Lipid and Lipoprotein Parameters:

LDL-C (by tertile),

HDL-C (by tertile),

TG (by tertile),

TG≥150 mg/dL,

TG≥200 mg/dL and TG<200 mg/dL, combined highest tertile for TG and lowest tertile for HDL-C,

hs-CRP (≤3 mg/L and >3 mg/L),

Apo B (by tertile),

non-HDL-C (by tertile)

The consistency of the treatment effects in subgroups will be assessed for the primary and key secondary efficacy endpoints. For each subgroup variable, a Cox proportional hazard model with terms for treatment, stratification factors (with the exception of those subgroup variables related to the stratification factors, i.e., CV risk category), subgroup, and treatment-by-subgroup interaction will be performed. The main treatment effect will not be tested with this model. P-values for testing the interaction terms will be provided.

Interim Efficacy Analysis

One interim analysis will be performed for the primary efficacy endpoint using best available data (adjudicated events and site reported endpoints) based on data when approximately 60% of the total number of primary endpoint events is reached. The interim analysis will be based on a group sequential design that includes early stopping rules for benefit while preserving the overall Type I error rate (O'Brien-Fleming). This allows for interim analysis and preserves the overall Type I error probability of α=0.05 for the primary endpoint.

Approximately 1612 primary efficacy endpoint events are planned to be observed during the trial, based on sample size calculation assumptions. Therefore, the interim analysis will occur after at least 967 primary efficacy endpoint events have been observed. According to this boundary, the critical p-value at the interim analysis has to be p≤0.0076, resulting in the final evaluation p-value of 0.0476.

The interim results of the study will be monitored by an independent DMC. The analyses will be performed by the independent statistical group unblinded to the treatment assignment. The results will be reported only to the DMC. The unblinded information will not be released to sponsor under any circumstance before the completion of the study. Specific statistical guidelines for data monitoring will be discussed and formalized in a separate Interim Statistical Analysis Plan and DMC Charter.

Analysis of Safety

All analyses of safety will be conducted on the safety population, which is defined as all randomized patients who receive at least one dose of study drug. The safety assessment will be based on the frequency of adverse events, physical exams, vital signs and safety laboratory tests.

Adverse events with new onset during the study between the initiation of study drug and 30 days after the last dose of study drug for each patient will be considered treatment-emergent (TEAEs). This will include any AE with onset prior to initiation of study drug and increased severity after the treatment initiation.

Treatment-emergent adverse events will be summarized by system organ class and preferred term, and by treatment. This will include overall incidence rates (regardless of severity and relationship to study drug), and incidence rates for moderate or severe adverse events. A summary of SAEs and adverse events leading to early discontinuation from the study will be presented through data listings.

Safety laboratory tests and vital signs will be summarized by post-treatment change from baseline for each of the parameters using descriptive statistics by treatment group. Those patients with significant laboratory abnormalities will be identified in data listings. Additional safety parameters will be summarized in data listings.

Sample Size Determination

Sample size estimation is based on the assumption that the primary composite endpoint (time from randomization to the first occurrence of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina requiring hospitalization) would be relatively reduced by 15%, from an event rate by 4 years of 23.6% in the placebo group to 20.5% in the AMR101 group. It is expected that a minimum of 1612 primary efficacy endpoint events will be required during the study. A total of approximately 6990 patients are needed to be able to detect this difference at 4.76% significance level (because of the interim analysis described in Section 12.2.4.6) and with 90% power, assuming an 18-month enrollment period and a median follow-up of 4 years. The current sample size calculation is based on an estimated placebo yearly event rate of 5.9% (23.6% over 4 years). To protect against the possibility that the actual placebo event rate is lower than estimated, an extra 1000 patients will be enrolled (approximately 7990 patients in total). By adding the extra 1000 patients, the event rate in the placebo group could be 5.2% per year (20.8% over 4 years) without having to modify the other sample size assumptions.

Since this is an events-driven trial, the 'sample size' is the number of events rather than the number of patients. The number of events that occur depends primarily on three factors: how many patients are enrolled, the combined group event rate, and how long the patients are followed. Because of the difficulty in predicting the combined event rate, the sponsor will monitor that event rate as the trial progresses. If the combined event rate is less than anticipated, either increasing the number of patients, extending the length of follow-up, or a balance of adjusting both factors may be necessary to achieve the sample size of 1612 events.

Before completing the enrollment phase of the trial, i.e. approximately 3- to 6-months prior to the projected enrollment of the 7990th patient, the actual event rate based on pooled, blinded accumulation of primary efficacy endpoint events will be calculated and plotted. If those analyses suggest the number of patients with at least 1 adjudicated, primary event (and appropriately accounting for patients with potential primary events for which the adjudication process is then incomplete) is consistent with projections,

then the study could continue toward the protocol-specified target enrollment of 7990 patients. However, if the number of such events appears less than, and inconsistent with projections, the Sponsor will consider (under blinded conditions) re-calculating the number of patients needed to achieve the target number of events within the desired timeline or extend the follow-up period. If the projected increase in number of patients is ≤25% of the original 7990 target population, the Sponsor may, with documented approval of both the REDUCE-IT Steering Committee (SC) and the Data Monitoring Committee (DMC), extend enrollment to the revised target number without need for an additional protocol amendment. Under those conditions, all principal investigators, ethics committees, and regulatory authorities associated with the protocol will be promptly notified of the action. Should the projected increase in number of patients be more than 25% above the original 7990 target (i.e. more than 1998 additional patients) a formal protocol amendment will be initiated.

If the number of patients to be studied is increased, the enrollment phase will be extended to allow enrollment of the additional patients.

At completion of study enrollment, the actual number of patients randomized may vary from the target number (either original or revised) as a result of the inherent lag between the date the last patient started screening and the date the last patient was randomized.

Monitoring, Data Management, and Record Keeping

Data Management

Data Handling

Data will be recorded at the site on CRFs. All entries on a CRF are ultimately the responsibility of the Investigator, who is expected to review each form for completeness and accuracy before signing. A CRF must be completed for each randomized patient. The CRFs and source documents must be made available to the Sponsor and/or its designee.

Record Keeping

The Investigator must maintain all documents and records, originals or certified copies of original records, relating to the conduct of this trial, and necessary for the evaluation and reconstruction of the clinical trial. This documentation includes, but is not limited to protocol, CRFs, AE reports, patient source data (including records of patients, patient visit logs, clinical observations and findings), correspondence with health authorities and IRB, consent forms, inventory of study product, Investigator's curriculum vitae, monitor visit logs, laboratory reference ranges and laboratory certification or quality control procedures, and laboratory director curriculum vitae.

The Investigator and affiliated institution should maintain the trial documents as required by the applicable regulations. The Investigator and affiliated institution should take measures to prevent accidental or premature destruction of documents. Clinical trial documents must be kept in the clinical site's archives indefinitely, unless written authorization is obtained from the Sponsor.

Direct Access to Source Data/Documents

The investigator and research institution agree that the Sponsor, their representatives and designees, the IRB or IEC, and representatives from worldwide regulatory agencies will have the right, both during and after the clinical trial, to review and inspect pertinent medical records related to the clinical trial.

Quality Control and Quality Assurance

The Sponsor and/or its designee(s) will perform quality control and quality assurance checks of all clinical trials that it sponsors. Before the enrollment of any patient in this study, the Sponsor or its designee will review with the investigator and site personnel the following documents: protocol, Investigator's Brochure, CRFs and procedures for their completion, the informed consent process, and the procedure for reporting SAEs. Site visits will be performed by the Sponsor and/or its designees. During these visits, information recorded on the CRFs will be verified against source documents and requests for clarification or correction may be made. After the CRF data is entered by the site, the Sponsor or designee will review for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical trial. If necessary, requests for clarification or correction will be sent to investigators.

By signing the protocol, the Sponsor agrees directly or through its designee(s) to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice (GCP), International Conference on Harmonization (ICH) and other applicable regulations.

Completion of Study

The end of the study will be at the time of the last patient-last visit of the follow-up period of the study. The IRB and IEC will be notified about the end of the study according to country-specific regulatory requirements.

TABLE 1

SCHEDULE OF PROCEDURES

	Screening								
	Up to 42 days before Day 0	If a Visit 1.1 takes place, Visit 1 may occur up to 60 days before Day 0 [2]	Follow-Up (FU) [13]						
			0	120 ± 10	360 ± 10	720 ± 10	1080 ± 10	1440 ± 10	1800 + 30
Study Day			0						
Months of FU			0	4	12	24	36	48	60
Years of FU			0	0.33	1	2	3	4	5
Visit #	1	1.1	2	3	4	5	6	7	LV [14]

TABLE 1-continued

SCHEDULE OF PROCEDURES

	Screening		Follow-Up (FU) [13]						
Study Day	Up to 42 days before Day 0	If a Visit 1.1 takes place, Visit 1 may occur up to 60 days before Day 0 [2]	0	120 ± 10	360 ± 10	720 ± 10	1080 ± 10	1440 ± 10	1800 + 30
Study Procedures:									
Informed Consent	X								
Medical, Surgical & Family History	X								
Demographics	X								
Evaluate inclusion/ exclusion criteria	X [1]	X [3]	X						
Physical Examination			X	X	X	X	X	X	X
Weight, Height [4]	X		X	X	X	X	X	X	X
Vital Signs [5]	X	X	X	X	X	X	X	X	X
Waist Circumference			X			X			X
12-Lead ECG	X		X		X	X	X	X	X
Urine pregnancy test [6]	X		X						
Concomitant Meds	X	X	X	X	X	X	X	X	X
Randomization			X						
Dosing at the Research Site [7]			X	X	X	X	X	X	
Efficacy events				X	X	X	X	X	X
AE Evaluations			X	X	X	X	X	X	X
Compliance Check [8]				X	X	X	X	X	X
Chemistry and hematology [9]	X	X [3]	X	X	X	X	X	X	X
Fasting lipid profile [10]	X	X [3]	X	X	X	X	X	X	X
Genetic testing [11]			X						
Biomarkers: hs-CRP, apo B, hsTNT			X			X			X
Fasting blood sample for archiving [12]			X		X	X	X	X	X

What is claimed is:

1. A method of reducing risk of cardiovascular death in a subject with established cardiovascular disease, the method comprising administering to said subject about 4 g of ethyl icosapentate per day for a period effective to reduce risk of cardiovascular death in the subject.

2. The method of claim **1**, wherein the subject has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL and a fasting baseline LDL-C level of about 40 mg/dL to about 100 mg/dL.

3. The method of claim **1**, wherein the ethyl icosapentate is present in a pharmaceutical composition and the ethyl icosapentate comprises at least about 96 wt. % of all omega-3 fatty acids in the pharmaceutical composition.

4. The method of claim **3**, wherein about 1 g of the pharmaceutical composition is present in each of 4 capsules.

5. The method of claim **1**, wherein said period ends at least 2 years after initial administration of the ethyl icosapentate to the subject.

6. The method of claim **1**, wherein the subject is on statin therapy.

7. The method of claim **1**, wherein the subject has a triglyceride level of at least 135 mg/dL and is on statin therapy.

* * * * *

FORM 19. Certificate of Compliance with Type-Volume Limitations **Form 19**
July 2020

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATIONS

Case Number: 23-1169

Short Case Caption: Amarin Pharma, Inc. v. Hikma Pharmaceuticals USA Inc.

Instructions: When computing a word, line, or page count, you may exclude any items listed as exempted under Fed. R. App. P. 5(c), Fed. R. App. P. 21(d), Fed. R. App. P. 27(d)(2), Fed. R. App. P. 32(f), or Fed. Cir. R. 32(b)(2).

The foregoing filing complies with the relevant type-volume limitation of the Federal Rules of Appellate Procedure and Federal Circuit Rules because it meets one of the following:

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☐ the filing contains _____ pages / _____ words / _____ lines of text, which does not exceed the maximum authorized by this court's order (ECF No. _____).

Date: 03/21/2023

Signature: /s/Nathan K. Kelley

Name: Nathan K. Kelley